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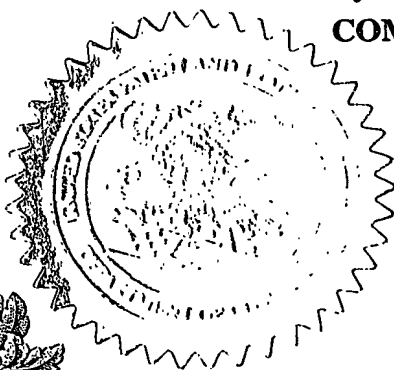
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APPLICATION NUMBER: 10/662,613

FILING DATE: September 15, 2003

CA /04/ 1674

By Authority of the  
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UTILITY  
PATENT APPLICATION  
TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	P05562US00
First Inventor	FARID, Abdol Hossain, et al.
Title	INSULIN-LIKE GROWTH FACTOR-1
Express Mail Label No.	EV 330573076 US

## APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

## ADDRESS TO:

Mail Stop Patent Application  
Commissioner for Patents  
P.O. Box 1450  
Alexandria VA 22313-145003940 U.S. PTO  
10/662613

09/15/03

1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)  
(Submit an original and a duplicate for fee processing)
2. ☐ Applicant claims small entity status.  
See 37 CFR 1.27.
3. ☒ Specification [Total Pages 72]  
(preferred arrangement set forth below)
  - Descriptive title of the invention
  - Cross Reference to Related Applications
  - Statement Regarding Fed sponsored R & D
  - Reference to sequence listing, a table, or a computer program listing appendix
  - Background of the Invention
  - Brief Summary of the Invention
  - Brief Description of the Drawings (if filed)
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure
4. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 83]
5. Oath or Declaration [Total Sheets       ]
  - a. ☐ Newly executed (original or copy)
  - b. ☐ Copy from a prior application (37 CFR 1.63(d))  
(for continuation/divisional with Box 18 completed)
  - i. ☐ **DELETION OF INVENTOR(S)**  
Signed statement attached deleting inventor(s)  
name in the prior application, see 37 CFR  
1.63(d)(2) and 1.33(b).
6. ☒ Application Data Sheet. See 37 CFR 1.76

7. ☐ CD-ROM or CD-R in duplicate, large table or  
Computer Program (Appendix)
8. Nucleotide and/or Amino Acid Sequence Submission  
(if applicable, all necessary)
  - a. ☒ Computer Reader Form (CRF)

## b. Specification Sequence Listing on:

i. ☐ CD-ROM or CD-R (2 copies); orii. ☒ Paperc. ☒ Statements verifying identity of above copies

## ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement ☐ Power of  
(when there is an assignee) Attorney
11. ☐ English Translation Document (if applicable)
12. ☐ Information Disclosure ☐ Copies of IDS  
Statement (IDS)/PTO-1449 Citations
13. ☐ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
15. ☐ Certified Copy of Priority Document(s)  
(if foreign priority is claimed)
16. ☐ Nonpublication Request under 35 U.S.C. 122  
(b)(2)(B)(i). Applicant must attach form PTO/SB/35  
or its equivalent.
17. ☐ Other: .....

18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: .....

Prior application information:

Examiner: .....


Art Unit: .....

For CONTINUATION OF DIVISIONAL APPS only; The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 6b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

## 19. CORRESPONDENCE ADDRESS

☒ Customer Number: 22885 OR ☐ Correspondence address below

Name			
Address			
City	State	Zip Code	
Country	Telephone	Fax	

Name (Print/Type)	HEIDI SEASE NEBEL	Registration No. (Attorney/Agent)	37,719
Signature		Date	9/15/03

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Express Label No. EV 330573076 US

PTO/SB/17 (05-03)

Approved for use through 04/30/2003. OMB 0651-0032  
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**FEE TRANSMITTAL**  
**for FY 2003**

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT

(\$) 2,250.00

**Complete if Known**

Application Number

Filing Date

First Named Inventor

FARID, Abdol Hossain, et al.

Examiner Name

Art Unit

Attorney Docket No.

P05562US00

**METHOD OF PAYMENT (check all that apply)**☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit Account:Deposit Account Number  
Deposit Account Name

26-0084

McKee, Voorhees &amp; Sease, P.L.C.

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) during the pendency of this application☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 750	2001 375	Utility filing fee	750.00
1002 330	2002 165	Design filing fee	
1003 520	2003 260	Plant filing fee	
1004 750	2004 375	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	
<b>SUBTOTAL (1)</b>			<b>(\$) 750.00</b>

**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

Total Claims	Extra Claims	Fee from below	Fee Paid
80	20** = 60	18	1080.
Independent Claims	8	3** = 5	84
Multiple Dependent			

<u>Large Entity</u>		<u>Small Entity</u>		<u>Fee Description</u>
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

\*\*or number previously paid, if greater; For Reissues, see above

**FEE CALCULATION (continued)****3. ADDITIONAL FEES**

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 410	2252 205	Extension for reply within second month	
1253 930	2253 465	Extension for reply within third month	
1254 1,450	2254 725	Extension for reply within fourth month	
1255 1,970	2255 985	Extension for reply within fifth month	
1401 320	2401 160	Notice of Appeal	
1402 320	2402 160	Filing a brief in support of an appeal	
1403 280	2403 140	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,300	2453 650	Petition to revive - unintentional	
1501 1,300	2501 650	Utility issue fee (or reissue)	
1502 470	2502 235	Design issue fee	
1503 630	2503 315	Plant issue fee	
1480 130	1480 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1808 180	1808 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 750	2809 375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 750	2810 375	For each additional invention to be examined (37 CFR 1.129(b))	
1801 750	2801 375	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify)

\*Reduced by Basic Filing Fee Paid

**SUBTOTAL (3)** (\$) 0**SUBMITTED BY**

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515-288-3667

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Date

9/18/03

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

TITLE: INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) POLYMORPHIC ALLELES AND USE OF THE SAME TO IDENTIFY DNA MARKERS FOR REPRODUCTIVE LONGEVITY

5 BACKGROUND OF THE INVENTION

Genetic mutations are the basis of evolution and genetic diversity. Genetic markers represent specific loci in the genome of a species, population or closely related species, and sampling of different genotypes at these marker loci reveals genetic variation. The genetic variation at marker loci can then be described and applied to genetic studies, commercial  
10 breeding, diagnostics, and cladistics. Genetic markers have the greatest utility when they are codominant, highly heritable, multi-allelic, and numerous. Most genetic markers are heritable because their alleles are determined by the nucleotide sequence of DNA which is highly conserved from one generation to the next, and the detection of their alleles is unaffected by the natural environment. Markers have multiple alleles because, in the  
15 evolutionary process, rare, genetically-stable mutations in DNA sequences defining marker loci arose and were disseminated through the generations along with other existing alleles. The highly conserved nature of DNA combined with rare occurrences of stable mutations allows genetic markers to be both predictable and discerning of different genotypes. The repertoire of genetic-marker technologies today allows multiple technologies to be used  
20 simultaneously in the same project. The invention of each new genetic-marker technology and each new DNA polymorphism adds additional utility to genetic markers. Many genetic-marker technologies exist. Some examples are restriction-fragment-length polymorphism (RFLP) Bostein et al (1980) *Am J Hum Genet* 32:314-331; single-strand conformation polymorphism (SSCP) Fischer et al. (1983) *Proc Natl Acad Sci USA*  
25 80:1579-1583, Orita et al. (1989) *Genomics* 5:874-879; amplified fragment-length polymorphism (AFLP) Vos et al. (1995) *Nucleic Acids Res* 23:4407-4414; microsatellite or single-sequence repeat (SSR) Weber J L and May P E (1989) *Am J Hum Genet* 44:388-396; random-amplified polymorphic DNA (RAPD) Williams et al (1990) *Nucleic Acids Res* 18:6531-6535; sequence tagged site (STS) Olson et al. (1989) *Science* 245:1434-1435;  
30 genetic-bit analysis (GBA) Nikiforov et al (1994) *Nucleic Acids Res* 22:4167-4175; allele-specific polymerase chain reaction (ASPCR) Gibbs et al. (1989) *Nucleic Acids Res* 17:2437-2448, Newton et al. (1989) *Nucleic Acids Res* 17:2503-2516; nick-translation



PCR (e.g., TAQMAN<sup>TM</sup>) Lee et al. (1993) *Nucleic Acids Res* 21:3761-3766; and allele-specific hybridization (ASH) Wallace et al. (1979) *Nucleic Acids Res* 6:3543-3557, (Sheldon et al. (1993) *Clinical Chemistry* 39(4):718-719) among others. Each technology has its own particular basis for detecting polymorphisms in DNA sequence.

5        The ability to follow a specific favorable genetic allele involves a novel and lengthy process of the identification of a DNA molecular marker for a major effect gene. The marker may be linked to a single gene with a major effect or linked to a number of genes with additive effects. DNA markers have several advantages; segregation is easy to measure and is unambiguous, and DNA markers are co-dominant, i.e., heterozygous and  
10   homozygous animals can be distinctively identified. Once a marker system is established selection decisions could be made very easily, since DNA markers can be assayed any time after a tissue or blood sample can be collected from the individual infant animal, or even an embryo.

      Poor reproductive performance is one of the major causes for culling in dairy  
15   (Beaudeau et al. 1995; Durr et al. 1997; Kulak et al. 1997; Bascom and Young 1998) and beef cattle (Tanida et al. 1988), and leads to a decrease in profitability (Tanida et al. 1988; Beaudeau et al. 1995; Kulak et al. 1997; Bascom and Young 1998). The highest level of profitability in a dairy herd is achieved when high yielding cows are maintained in the herd for several lactations (Gill and Allaire 1976; Allaire and Gibson 1992; Kulak et al. 1997).

20   An increase in length of production from 3 to 4 lactations increases milk yield per lactation and profit per year by 11 and 13% respectively (Strandberg 1996). Reproductive longevity is even more important in beef cattle, sheep, swine and fur bearing animals, where replacement cost is, after nutrition, the second highest source of expenditure. Clearly, improving reproductive longevity offers one of the greatest opportunities for increasing  
25   productive efficiency and economic return in the multi-billion dollar livestock industry in the world. This is illustrated by the fact that reproductive longevity is included in the national dairy genetic evaluation systems in Canada (herd life) and the U.S. (production life).

      Moderate variation exists for reproductive longevity within and among different  
30   breeds of cattle (Silva et al. 1986; Smith and Quass 1984; Bailey 1991; Arthur et al. 1993), suggesting the possibility for genetic improvement in this trait. However, despite its

obvious economic importance, it is difficult to improve reproductive longevity through conventional breeding methods because of the low heritability of this trait (Smith and Quass 1984; Tanida et al. 1988; Boldman et al. 1992; VanRaden and Klaaskate 1993) and the long time necessary to obtain information on reproductive longevity in livestock.

- 5 Attempts to improve reproductive longevity of dairy cattle through indirect selection, such as the use of 'type traits' that are measured early in life, has been ineffective (Smith and Quass 1984; Boldman et al. 1992; VanRaden and Klaaskate 1993).

The above limitations make reproductive longevity an ideal candidate trait for the use of DNA markers (Lande and Thompson 1990), which would provide a means of  
10 identification of animals with superior breeding value at an early age on the basis of a simple laboratory test. Developing DNA markers for reproductive longevity is, however, a difficult and time-consuming task in long-lived livestock resources. A logical strategy would involve identification of candidate genes in a mammalian model with a short generation interval and later validating them in livestock (Copeland et al. 1993). This is  
15 especially true in the case of genes that control reproductive longevity and life span (Rose and Nusbaum 1994), since direct selection for prolonged reproductive age in large mammals is very time consuming and prohibitively expensive. The genes identified in animals will be putative candidates for the development of DNA markers for reproductive longevity in other species.

- 20 Although there are several reports on the quantitative genetics aspects of reproductive longevity in livestock (VanRaden and Klaaskate 1993; Smith and Quass 1984; Kulak *et al.* 1997; Bascom and Young 1998), little information is available on the genetic control of this trait in any mammalian species. Most of the available information on the genetic control of reproductive longevity and life span has been obtained on simple  
25 organisms, such as *Drosophila* and *Caenorhabditis elegans* (*C. elegans*). In *C. elegans*, for example, the *daf* genes (*daf-2*, *-12*, *-16*, *-18* *-23*), which are components of the IGF-1R signaling cascade, have been shown to control the regulation of metabolism, development, reproduction and life span (Lakowski and Hekimi 1996; Apfeld and Kenyon 1998; Hekimi *et al.* 1998). Also, there is a positive relationship between life span and reproduction in *C.*  
30 *elegans* (Hsin and Kenyon 1999) and among mammals (Packer *et al.* 1998; Tissenbaum and Ruvkun 1998). Although information on lower organisms is useful, their usefulness in

mammals should be assessed in an appropriate mammalian model that exhibits widely contrasting reproductive longevity phenotypes.

5 The use of DNA markers will facilitate the identification of animals that are genetically prone to a) reproduce longer than the average and, separately b) those that have a higher likelihood, compared with the average, of conceiving during lactation (sustained lactation and pregnancy stress). The marker may be directly involved in prolonging reproductive life, or may be linked to a single gene with a major effect, or may be linked to a number of genes with additive effects on animals' phenotype. Their segregation is easy to measure and is unambiguous, and DNA markers are co-dominant, i.e., heterozygous and  
10 homozygous animals can be distinctively identified. Once a marker system is established, selection decisions can be made easily, since DNA markers can be assayed any time after a tissue or blood sample can be collected from the individual infant animal, or even an embryo.

For the foregoing reasons, there is a need for a method of selecting animals with  
15 improved reproductive longevity and/or ability to better sustain stress factors. More particularly, a need for identifying markers which may be used to improve economically beneficial characteristics in animals by identifying and selecting animals with these favorable characteristics at the genetic level.

Therefore, an object of the present invention is to provide a method of identifying  
20 polymorphisms in the IGF-1R gene which are indicative of reproductive longevity in mammals and their ability to sustain performance in combination with stress factors such as lactation, pregnancy, and health status.

Another object of the invention is to provide assays for determining the presence of these genetic markers.

25 A further object of the invention is to provide methods for screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity and the ability to sustain performance under stress, which increases the accuracy of selection and breeding methods.

Yet another object of the invention is to provide PCR amplification and detection  
30 tests which will greatly expedite the determination of presence of the markers.

A still further object of the invention is to provide a method for determining the haplotype of the IGF-1R gene indicative of reproductive longevity and the ability to sustain performance under stress.

5 Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by the practice of the invention. The objects and advantages of the invention will be attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

## 10 BRIEF SUMMARY OF THE INVENTION

This invention relates to the discovery of alternate forms of the insulin-like growth factor-1 receptor (IGF-1R) gene which are useful as a genetic markers associated with reproductive longevity and the ability to better sustain stress factors in animals such as lactation and pregnancy in animals.

15 According to an embodiment of the present invention there are provided methods for identifying a polymorphism in an animal. One embodiment includes a method for genetically identifying an animal comprising obtaining a sample of genetic material from an animal and assaying for the presence of a polymorphism in the insulin-like growth factor 1 receptor gene (IGF-1R), wherein said polymorphism is associated with reproductive  
20 longevity and/or ability to better sustain stress factors such as lactation and pregnancy stress.

A further embodiment includes a method for screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity and ability to sustain stress factors such as lactation and pregnancy stress. These methods include  
25 obtaining a genetic sample from the animal. The methods can further include assaying for the presence or absence of a polymorphism in the IGF-1R gene associated with reproductive longevity and/or the ability to sustain stress factors in animals such as lactation and pregnancy.

Further embodiments of the invention can include amplifying the gene or a region  
30 of the gene, which contains at least one polymorphism. Since one of the polymorphisms may involve changes in the amino acid composition of the IGF-1R protein, assay methods

may even involve ascertaining the amino acid composition of these proteins. Methods for this type of purification and analysis typically involve isolation of the protein through means including fluorescence tagging with antibodies, separation and purification of the protein (i.e., through reverse phase HPLC system), and use of an automated protein  
5 sequencer to identify the amino acid sequence present. Protocols for this assay are standard and known in the art and are disclosed in Ausubel et al. (eds.), *Short Protocols in Molecular Biology* 4<sup>th</sup> ed. (John Wiley and Sons 1999).

Another embodiment includes a method for determining the haplotype of the IGF-1R gene of an animal wherein the haplotype is indicative of reproductive longevity and/or  
10 ability to sustain stress factors.

In a preferred embodiment, a sample of genetic material is obtained from an animal and the sample is analyzed to determine the presence or absence of a polymorphism in the IGF-1R gene, which is correlated with reproductive longevity and/or ability to sustain stress factors such as lactation and pregnancy stress.

15 As is well known to those of skill in this art, a variety of techniques may be utilized when comparing nucleic acid molecules for sequence differences. These include by way of example, restriction fragment length polymorphism analysis, heteroduplex analysis, single-strand conformation polymorphism analysis, denaturing gradient electrophoresis and temperature gradient electrophoresis.

20 In a preferred embodiment the polymorphism is a 12-bp deletion and two restriction fragment length polymorphism and the assay comprises identifying the animal's IGF-1R gene from isolated genetic material; exposing the gene to a restriction enzyme that yields restriction fragments of the gene of varying length; separating the restriction fragments to form a restriction pattern, such as by electrophoresis or HPLC separation; and comparing  
25 the resulting restriction fragment pattern from a IGF-1R gene that is either known to have or not to have the desired marker.

In a most preferred embodiment the gene is isolated by the use of primers and DNA polymerase to amplify a specific region of the gene which contains the polymorphism. Next the amplified region is digested with a restriction enzyme and fragments are again  
30 separated. Visualization of the RFLP pattern is by simple staining of the fragments, or by labeling the primers or the nucleoside triphosphates used in amplification.

It expected that with no more than routine testing as described herein this marker can be applied to different animal species to select for reproductive longevity and/or sustained performance in a situation with stress caused by lactation, pregnancy, or health status based on the teachings herein. Female animals of the same breed or breed cross or similar genetic lineage are bred, and the reproductive longevity and/or sustained lactation and pregnancy stress shown by each animal is determined and correlated. For other species in which sequences are available a BLAST comparison of the IGF-1R may be used to ascertain whether the particular allele disclosed herein is present.

The term "analogous polymorphism" shall be a polymorphism which is the same as any of those disclosed herein as determined by BLAST comparisons.

The following terms are used to describe the sequence relationships between two or more nucleic acids or polynucleotides: (a) "reference sequence", (b) "comparison window", (c) "sequence identity", (d) "percentage of sequence identity", and (e) "substantial identity".

(a) As used herein, "reference sequence" is a defined sequence used as a basis for sequence comparison. In this case the Reference is the IGF-1R sequence. A reference sequence may be a subset or the entirety of a specified sequence; for example, as a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence.

(b) As used herein, "comparison window" includes reference to a contiguous and specified segment of a polynucleotide sequence, wherein the polynucleotide sequence may be compared to a reference sequence and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Generally, the comparison window is at least 20 contiguous nucleotides in length, and optionally can be 30, 40, 50, 100, or longer. Those of skill in the art understand that to avoid a high similarity to a reference sequence due to inclusion of gaps in the polynucleotide sequence, a gap penalty is typically introduced and is subtracted from the number of matches.

Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman, *Adv. Appl. Math.* 2:482 (1981); by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48:443 (1970); by the search

for similarity method of Pearson and Lipman, *Proc. Natl. Acad. Sci.* 85:2444 (1988); by computerized implementations of these algorithms, including, but not limited to: CLUSTAL in the PC/Gene program by Intelligenetics, Mountain View, California; GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package,

- 5 Genetics Computer Group (GCG), 575 Science Dr., Madison, Wisconsin, USA; the CLUSTAL program is well described by Higgins and Sharp, *Gene* 73:237-244 (1988); Higgins and Sharp, *CABIOS* 5:151-153 (1989); Corpet, et al., *Nucleic Acids Research* 16:10881-90 (1988); Huang, et al., *Computer Applications in the Biosciences* 8:155-65 (1992), and Pearson, et al., *Methods in Molecular Biology* 24:307-331 (1994). The
- 10 BLAST family of programs which can be used for database similarity searches includes: BLASTN for nucleotide query sequences against nucleotide database sequences; BLASTX for nucleotide query sequences against protein database sequences; BLASTP for protein query sequences against protein database sequences; TBLASTN for protein query sequences against nucleotide database sequences; and TBLASTX for nucleotide query
- 15 sequences against nucleotide database sequences. See, *Current Protocols in Molecular Biology*, Chapter 19, Ausubel, et al., Eds., Greene Publishing and Wiley-Interscience, New York (1995).

Unless otherwise stated, sequence identity/similarity values provided herein refer to the value obtained using the BLAST 2.0 suite of programs using default parameters.

- 20 Altschul et al., *Nucleic Acids Res.* 25:3389-3402 (1997). Software for performing BLAST analyses is publicly available, e.g., through the National Center for Biotechnology-Information (<http://www.ncbi.nlm.nih.gov/>).

- This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy
- 25 some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative
- 30 scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues;

always  $< 0$ ). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity  $X$  from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters  $W$ ,  $T$ , and  $X$  determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength ( $W$ ) of 11, an expectation ( $E$ ) of 10, a cutoff of 100,  $M=5$ ,  $N=-4$ , and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength ( $W$ ) of 3, an expectation ( $E$ ) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin & Altschul, *Proc. Natl. Acad. Sci. USA* 90:5873-5787 (1993)). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ( $P(N)$ ), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance.

BLAST searches assume that proteins can be modeled as random sequences. However, many real proteins comprise regions of nonrandom sequences which may be homopolymeric tracts, short-period repeats, or regions enriched in one or more amino acids. Such low-complexity regions may be aligned between unrelated proteins even though other regions of the protein are entirely dissimilar. A number of low-complexity filter programs can be employed to reduce such low-complexity alignments. For example, the SEG (Wooten and Federhen, *Comput. Chem.*, 17:149-163 (1993)) and XNU (Claverie and States, *Comput. Chem.*, 17:191-201 (1993)) low-complexity filters can be employed alone or in combination.

(c) As used herein, "sequence identity" or "identity" in the context of two nucleic acid or polypeptide sequences includes reference to the residues in the two sequences which are the same when aligned for maximum correspondence over a specified comparison window. When percentage of sequence identity is used in reference to proteins it is recognized that residue positions which are not identical often differ by conservative



amino acid substitutions, where amino acid residues are substituted for other amino acid residues with similar chemical properties (e.g. charge or hydrophobicity) and therefore do not change the functional properties of the molecule. Where sequences differ in conservative substitutions, the percent sequence identity may be adjusted upwards to correct for the conservative nature of the substitution. Sequences which differ by such conservative substitutions are said to have "sequence similarity" or "similarity". Means for making this adjustment are well-known to those of skill in the art. Typically this involves scoring a conservative substitution as a partial rather than a full mismatch, thereby increasing the percentage sequence identity. Thus, for example, where an identical amino acid is given a score of 1 and a non-conservative substitution is given a score of zero, a conservative substitution is given a score between zero and 1. The scoring of conservative substitutions is calculated, e.g., according to the algorithm of Meyers and Miller, *Computer Applic. Biol. Sci.*, 4:11-17 (1988) e.g., as implemented in the program PC/GENE (Intelligenetics, Mountain View, California, USA).

(d) As used herein, "percentage of sequence identity" means the value determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

(e) The term "substantial identity" of polynucleotide sequences means that a polynucleotide comprises a sequence that has at least 70% sequence identity, preferably at least 80%, more preferably at least 90% and most preferably at least 95%, compared to a reference sequence using one of the alignment programs described using standard parameters. One of skill will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and

the like. Substantial identity of amino acid sequences for these purposes normally means sequence identity of at least 60%, or preferably at least 70%, 80%, 90%, and most preferably at least 95%.

5 These programs and algorithms can ascertain the analogy of a particular polymorphism in a target gene to those disclosed herein. It is expected that this polymorphism will exist in other animals and use of the same in other animals than disclosed herein involved no more than routine optimization of parameters using the teachings herein.

10 It is also possible to establish linkage between specific alleles of alternative DNA markers and alleles of DNA markers known to be associated with a particular gene (e.g. the IGF-1R gene discussed herein), which have previously been shown to be associated with a particular trait. Thus, in the present situation, taking the IGF-1R gene, it would be possible, at least in the short term, to select for animals likely to produce one or more of the traits of reproductive longevity and/or the ability to better sustain stress caused by lactation  
15 and pregnancy, or alternatively against animals less likely to exhibit the traits of reproductive longevity and/or the ability to better sustain stress caused by lactation and pregnancy, indirectly, by selecting for certain alleles of a IGF-1R associated marker through the selection of specific alleles of alternative chromosome markers. As used herein the term "genetic marker" shall include not only the polymorphism disclosed by any  
20 means of assaying for the protein changes associated with the polymorphism, be they linked markers, use of microsatellites, or even other means of assaying for the causative protein changes indicated by the marker and the use of the same to influence the traits of reproductive longevity and/or the ability to sustain stress in an animal.

As used herein, often the designation of a particular polymorphism is made by the  
25 name of a particular restriction enzyme. This is not intended to imply that the only way that the site can be identified is by the use of that restriction enzyme. There are numerous databases and resources available to those of skill in the art to identify other restriction enzymes which can be used to identify a particular polymorphism. Two examples are:  
<http://www.geneseo.edu/~bio/> and <http://www.firstmarket.com/cutter/cut2.html>. In fact, as  
30 disclosed in the teachings herein there are numerous ways of identifying a particular

polymorphism or allele with alternate methods which may not even include a restriction enzyme, but which assay for the same genetic or proteomic alternative form.

5 The invention is intended to include these sequences as well as all conservatively modified variants thereof as well as those sequences which will hybridize under conditions of high stringency to the sequences disclosed. The term IGF-1R is used herein shall be interpreted to include these conservatively modified variants as well as those hybridized sequences.

10 The term "conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refer to those nucleic acids which encode identical or conservatively modified variants of the amino acid sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any  
15 of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations" and represent one species of conservatively modified variation. Every nucleic acid sequence herein that encodes a polypeptide also, by reference to the genetic code, describes every possible silent variation of the nucleic acid. One of ordinary skill will recognize that each codon in a nucleic acid (except AUG, which  
20 is ordinarily the only codon for methionine; and UGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide of the present invention is implicit in each described polypeptide sequence and is within the scope of the present invention.

25 As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Thus, any number of  
30 amino acid residues selected from the group of integers consisting of from 1 to 15 can be so altered. Thus, for example, 1, 2, 3, 4, 5, 7, or 10 alterations can be made.

Conservatively modified variants typically provide similar biological activity as the unmodified polypeptide sequence from which they are derived. For example, substrate specificity, enzyme activity, or ligand/receptor binding is generally at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the native protein for its native substrate. Conservative substitution tables providing functionally similar amino acids are well known in the art.

The following six groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Serine (S), Threonine (T);
- 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

See also, Creighton, *Proteins*, W.H. Freeman and Company (1984).

By "encoding" or "encoded", with respect to a specified nucleic acid, is meant comprising the information for translation into the specified protein. A nucleic acid encoding a protein may comprise non-translated sequences (e.g., introns) within translated regions of the nucleic acid, or may lack such intervening non-translated sequences (e.g., as in cDNA). The information by which a protein is encoded is specified by the use of codons. Typically, the amino acid sequence is encoded by the nucleic acid using the "universal" genetic code. However, variants of the universal code, such as are present in some plant, animal, and fungal mitochondria, the bacterium *Mycoplasma capricolum*, or the ciliate *Macronucleus*, may be used when the nucleic acid is expressed therein.

The term "stringent conditions" or "stringent hybridization conditions" includes reference to conditions under which a probe will hybridize to its target sequence, to a detectably greater degree than to other sequences (e.g., at least 2-fold over background). Stringent conditions are sequence-dependent and be different in different circumstances. By controlling the stringency of the hybridization and/or washing conditions, target sequences can be identified which are 100% complementary to the probe (homologous probing). Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity are detected (heterologous probing).

Generally, a probe is less than about 1000 nucleotides in length, optionally less than 500 nucleotides in length.

Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (*e.g.*, 10 to 50 nucleotides) and at least about 60°C for long probes (*e.g.*, greater than 50 nucleotides).

Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. One of ordinary skill is apprised in knowing that the time of the hybridization is dependent on the concentration of the probe. Exemplary low stringency conditions

include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl/0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 50°C. Exemplary high stringency conditions include

hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60 to 65°C for at least 15 minutes.

Specificity is typically the function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. For DNA-DNA hybrids, the  $T_m$  can be approximated from the equation of Meinkoth and Wahl, *Anal.*

*Biochem.*, 138:267-284 (1984):  $T_m = 81.5^\circ\text{C} + 16.6 (\log M) + 0.41 (\%GC) - 0.61 (\% \text{ form}) - 500/L$ ; where M is the molarity of monovalent cations, %GC is the percentage of guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the complementary target sequence hybridizes to a perfectly matched probe.  $T_m$  is reduced by about 1°C for each 1% of mismatching; thus,  $T_m$ , hybridization and/or wash conditions can be adjusted to hybridize to sequences of the desired identity. For example, if sequences with  $\geq 90\%$  identity are sought, the  $T_m$  can be decreased 10°C. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4°C lower than the

thermal melting point ( $T_m$ ); moderately stringent conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10°C lower than the thermal melting point ( $T_m$ ); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20°C lower than the thermal melting point ( $T_m$ ). Using the equation, hybridization and wash compositions, and desired  $T_m$ , those of ordinary skill will understand that variations in the stringency of hybridization and/or wash solutions are inherently described. If the desired degree of mismatching results in a  $T_m$  of less than 45°C (aqueous solution) or 32°C (formamide solution) it is preferred to increase the SSC concentration so that a higher temperature can be used. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Laboratory Techniques in Biochemistry and Molecular Biology—Hybridization with Nucleic Acids Probes*, Part I, Chapter 2, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995).

These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the nucleotide sequence of the insulin-like growth factor-1 receptor in mice (SEQ ID NO:1)(GenBank accession number AF056187).

Figure 2 depicts the amino acid sequence of the insulin-like growth factor-1 receptor in mice (SEQ ID NO:2)(GenBank protein id AAC12782.1).

Figure 3 depicts the mRNA sequence of insulin-like growth factor I receptor in mice (SEQ ID NO:3) (Genbank accession number XM\_133508).

Figure 4 depicts the alignment of exon 21 of the mouse IGF1-R sequences from Genbank accession number AF056187 (SEQ ID NO: 1) and Genbank accession number XM\_133508 (SEQ ID NO:3), and the amino acid sequence of this region (SEQ ID NO:4). The A to G substitution at position 3876 of the Genbank accession number AF056187 (*HpaII* site, locus B) is bolded and underlined. The 12 bp insertion/deletion is bolded and underlined. The junction of exon 20 and exon 21 is shown by "0".

Figure 5 depicts intron 16 (SEQ ID NO:5) of the mouse IGF1-R gene and the surrounding exons amplified by primers PSEQ16F (SEQ ID NO:12) and PSEQ16R (SEQ

ID NO:13), and its alignment with the mouse IGF1-R gene (Genbank accession number AC101879; SEQ ID NO:6). This sequence contains 102 bp of exon 16 (nucleotides 1 to 102), 283 bp of intron 16 (nucleotides 103 to 385) and 101 bp of exon 17 (nucleotides 386 to 486) of the mouse IFG1-R gene. Exon-intron junctions are shown by 0. The 'G'

5 insertion is at position 176 of SEQ ID NO:5 after nucleotide 56456 of SEQ ID NO:6 (Genbank accession number AC101879). This insertion is bolded and underlined. Note that SEQ ID NO:6 (Genbank accession number AC101879) is the reverse complement of other sequences of the IGF1-R in Genbank. The 'G' to 'A' substitution (*DpnII* site, locus A) is at position 331 of SEQ ID NO:5, corresponding to nucleotide 556303 of SEQ ID  
10 NO:6 (Genbank accession number AC101879). This nucleotide is bolded and underlined. The forward (PSEQ16F) and reverse (PSEQ16R) primers are underlined.

Figure 6 depicts mouse clone RP23-378H21, complete sequence (SEQ ID NO:6) (Genbank accession number AC101879).

Figure 7 depicts the nucleotide sequence of the insulin-like growth factor-1 receptor  
15 in pig (SEQ ID NO:7). cDNA sequence in lower case letters comes from Accession No. AB003362. Intron 9 sequence in lower case letters comes from Accession No. AJ491314. Intron sequence in upper case letters was derived from Applicants sequencing efforts.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

20 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Unless mentioned otherwise, the techniques employed or contemplated herein are standard methodologies well known to one of ordinary skill in the art.

As used herein, "reproductive longevity" means a biologically significant increase  
25 in the number of pregnancies and/or the duration of time an animal is capable of reproduction, relative to the mean of a given population, group or species.

As used herein, "the ability to sustain performance under stress" means a biologically significant increase in performance, in situations with stress, i.e., increase in the number of pregnancies and/or the duration of time while the animal is lactating and  
30 raising progeny, i.e., carrying a fetus while lactating at the same time, relative to the mean of a given population.

The insulin-like growth factor-1 receptor (IGF-1R) gene is a plasma membrane-bound disulfide-bonded heterotetrameric glycoprotein composed of two extracellular  $\alpha$ -subunits containing a ligand binding domain and two transmembrane  $\beta$ -subunits that include a cytoplasmic tyrosine kinase domain (Richards et al., 1998). The IGF-1R gene plays a vital role in growth and development in several different ways, such as mediating mitogenic and metabolic responses, maintaining transformed cell phenotype, protecting cells from apoptotic injuries, and inducing differentiation in certain cell types especially myoblasts, adipocytes, osteoblasts and cells of the central nervous system (Valentinis et al., 1999; Jin et al., 2000).

Binding of the ligand to IGF-1R leads to autophosphorylation of the  $\alpha$ -subunit and activation of the  $\beta$ -subunit tyrosine kinase domains resulting in phosphorylation of several intracellular proteins including insulin receptor substrates (IRS) and Shc with the subsequent trigger of multiple signaling cascades, for instance those of the Ras-Raf-MAP kinase network and phosphatidylinositol 3-kinase. The various effects may depend on specific domains of the receptor and the availability of different substrates (Peruzzi et al., 1999; Swantek et al., 1999; Valentinis et al., 1999; Xu et al., 1999; Soni et al., 2000).

The IGF-1R gene also plays a role in certain functions of other growth factors and hormones. There is evidence that a signal generated by a functional IGF-1R is required for the mitogenic effects of other growth factors, such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) (Swantek and Baserga, 1999). Furthermore, the estradiol-induced mitogenic effects in the mouse uterus and differentiation of rat adipocytes are dependent on the IGF-1R (Richards et al., 1998; Dieudonne et al., 2000).

According to an embodiment of the present invention variants or polymorphic sites in the IGF-1R gene have been located, and these genetic polymorphisms are associated with reproductive longevity and/or the ability to sustain stress factors such as lactation and pregnancy in mice. These four variants include an 'A' to 'G' substitution in intron 16, a 'G' nucleotide insertion in intron 16, an 'A' to 'G' substitution in exon 21, and a 12 bp-deletion in exon 21 which resulted in four fewer amino acids in the IGF-1R protein.

In another embodiment, assays are provided for detection of these different variants. The assays preferably involve amplifying the genomic DNA purified from blood, tissue,



semen, or other convenient source of genetic material by the use of primers and standard techniques, such as polymerase chain reaction (PCR).

5 A 12 bp deletion, PCR product was identified in mice. The PCR product can be sized in a variety of ways, such as by agarose or polyacrylamide gel electrophoresis, use of an automated DNA sequencer, or mass spectrometry.

10 An 'A' to 'G' substitution, at position 3876 of SEQ ID NO:1 (Genbank accession number AF056187) was identified in mice. The PCR product was digested with a restriction enzyme (e.g., *HpaII*) so as to yield gene fragments of varying lengths, as separating at least some of the fragments from others using agarose or polyacrylamide gel electrophoresis. Since the 'A' to 'G' substitution is 20 base pairs upstream from the 12-base pair deletion, both polymorphisms may be detected by the digestion of PCR product with the enzyme *HpaII*.

15 A 'G' to 'A' substitution (GGTC to GATC) was detected in intron 16 of the gene in mice. The 486 bp PCR product, spanning exons 16 and 17 and intron 16, was cut into 454 and 32 bp fragments (A<sub>1</sub> allele) by the enzyme *DpnII* (↑GATC). This nucleotide substitution resulted in the creation of a new recognition site for this enzyme, which cleaved the 454 bp fragment into 328 and 125 bp fragments (A<sub>2</sub> allele). In addition, sequence information revealed a 'G' nucleotide insertion in intron 16, 153 bp 5' to the above point mutation, but no restriction enzyme was found for discriminatory typing of this  
20 deletion.

In porcine, the following single nucleotide polymorphisms were found:

A 'G' to 'A' substitution, designated SNP16i27, at position 27 from the end of intron 16 was detected with an *AvaII* restriction site.

25 A 'G' to 'C' substitution, designated SNP16i73, was detected at position 73 from the end of intron 16. This nucleotide substitution resulted in a *MnII* restriction site.

A 'G' to 'A' substitution, designated SNP1772, was detected in exon 8. This nucleotide substitution resulted in a *TaqI* restriction site.

30 The polymorphisms in animals may also be identified using a variety of methods such as direct sequencing, and hybridizing with nucleotide probes labeled with radioactive or chemiluminescence. The probes may be sequences containing all or a portion of the IGF-1R gene containing the polymorphisms, which will be hybridized to the separated

digestion PCR products or digested genomic DNA. The polymorphism may also be detected by restriction fragment length polymorphism (RFLP) analysis, the single-stranded conformation polymorphism of the PCR product (SSCP-PCR), PCR amplification of specific alleles, the amplification of DNA target by PCR followed by single base extension which will be detected by fluorescent or radioactive substances or mass spectrometry, allelic discrimination during PCR, Genetic Bit Analysis, Pyrosequencing, oligonucleotide ligation assay, analysis of melting curves or other methods which detect differences in the length of a DNA fragment at this region or detect a single nucleotide substitution.

Another embodiment of the invention includes novel PCR primers comprising 4 to 30 contiguous bases on either side of the polymorphism to provide an amplification system allowing for detection of the polymorphism by PCR and identification of the fragments by standard methods. Any primers amplifying the region of the polymorphism may be used as taught herein and are also publically available.

The preferred primers for revealing the 12 bp deletion are PSEQDF: 5'-GGA GAT CAT CGG CAG CAT CAA G-3' (SEQ ID NO:8), wherein the 5' end is at position 3786 of the mouse IGF-1R gene and PSEQDR: 5'-GCC ATT CTC AGC CTT GTG TCC-3' (SEQ ID NO:9), wherein the 5' end is at the position 4002 of the mouse IGF-1R gene.

The preferred primers for revealing the A to G substitution in exon 21 of the IGF-1R gene are PSECAF: 5'-GCA TGT GCT GGC AGT ATA ACC-3' (SEQ ID NO:10), wherein the 5' end is at position 3743 of the IGF-1R gene and PSECAR: 5'-CAG AGG CCC ATG TCA GTT AAG (SEQ ID NO:11), wherein the 5' end is at position 4376 of the IGF-1R gene.

The preferred primers for revealing the G to A substitution in intron 16 of the IGF-1R gene are PSEQ16F: 5' AGA GTG GCC ATC AAG ACG GTA 3' (SEQ ID NO:12) and PSEQ16R: 5' GGC CTC AGA GAC CGG AGA T 3' (SEQ ID NO:13).

In porcine, the preferred primers for revealing SNP16i27 identified with an *Avall* restriction site are Primer 16: 5' - CCT CCG TGA TGA AGG AGT TC - 3' (SEQ ID NO:14) and Primer 17: 5' - TCA GTT CCA TGA TGA CCA GC - 3' (SEQ ID NO:15).

The preferred primers for revealing SNP16i73 identified with a *MnII* restriction site are Primer 16: 5' - CCT CCG TGA TGA AGG AGT TC - 3' (SEQ ID NO:16) and Primer 17: 5' - TCA GTT CCA TGA TGA CCA GC - 3' (SEQ ID NO:17).

The preferred primers for revealing SNP1772 identified with a *TaqI* restriction site are designated as Primer 9: 5' – GGA GTA TGA TGG GCA GGA T – 3' (SEQ ID NO:18) and Primer 8: 5' – GAA GCA TTG GTG CGA ATG TA – 3' (SEQ ID NO:19).

Computer programs available on the world wide web allows one of ordinary skill in the art to design other primers capable of amplifying polymorphic segments of the IGF-1R gene such as those shown above and depicted in Table 1. See Steve Rozen and Helen J. Skaletsky (2000) Primer3 on the WWW for general users and for biologist programmers. In: Krawetz S, Misener S (eds) *Bioinformatics Methods and Protocols: Methods in Molecular Biology*. Humana Press, Totowa, NJ, pp 365-386.

A further embodiment comprises a breeding method whereby assays of the above types are conducted on a plurality of gene sequences from different animals or animal embryos of various species to be selected from and, based on the results, certain animals are either selected or dropped out of the breeding program.

The following is a general overview of techniques which can be used to assay for the polymorphisms of the invention.

In the present invention, a sample of genetic material is obtained from an animal. Samples can be obtained from blood, tissue, semen, etc. Generally, peripheral blood cells are used as the source, and the genetic material is DNA. A sufficient amount of cells are obtained to provide a sufficient amount of DNA for analysis. This amount will be known or readily determinable by those skilled in the art. The DNA is isolated from the blood cells by techniques known to those skilled in the art.

#### Isolation and Amplification of Nucleic Acid

Samples of genomic DNA are isolated from any convenient source including saliva, buccal cells, hair roots, blood, cord blood, amniotic fluid, interstitial fluid, peritoneal fluid, chorionic villus, and any other suitable cell or tissue sample with intact nuclei. The cells can also be obtained from solid tissue as from a fresh or preserved organ or from a tissue sample or biopsy. The sample can contain compounds which are not naturally intermixed with the biological material such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

Methods for isolation of genomic DNA from these various sources are described in, for example, Kirby, *DNA Fingerprinting, An Introduction*, W.H. Freeman & Co. New York (1992). Genomic DNA can also be isolated from cultured primary or secondary cell cultures or from transformed cell lines derived from any of the aforementioned tissue samples.

Samples of animal RNA can also be used. RNA can be isolated from tissues expressing the IGF-1R gene as described in Sambrook et al., *supra*. RNA can be total cellular RNA, mRNA, poly A+ RNA, or any combination thereof. For best results, the RNA is purified, but can also be unpurified cytoplasmic RNA. RNA can be reverse transcribed to form DNA which is then used as the amplification template, such that the PCR indirectly amplifies a specific population of RNA transcripts. See, e.g., Sambrook, *supra*, Kawasaki et al., Chapter 8 in *PCR Technology*, (1992) *supra*, and Berg et al., *Hum. Genet.* 85:655-658 (1990).

#### PCR Amplification

The most common means for amplification is polymerase chain reaction (PCR), as described in U.S. Pat. Nos. 4,683,195, 4,683,202, 4,965,188 each of which is hereby incorporated by reference. If PCR is used to amplify the target regions in blood cells, heparinized whole blood should be drawn in a sealed vacuum tube kept separated from other samples and handled with clean gloves. For best results, blood should be processed immediately after collection; if this is impossible, it should be kept in a sealed container at 4°C until use. Cells in other physiological fluids may also be assayed. When using any of these fluids, the cells in the fluid should be separated from the fluid component by centrifugation.

Tissues should be roughly minced using a sterile, disposable scalpel and a sterile needle (or two scalpels) in a 5 mm Petri dish. Procedures for removing paraffin from tissue sections are described in a variety of specialized handbooks well known to those skilled in the art.

To amplify a target nucleic acid sequence in a sample by PCR, the sequence must be accessible to the components of the amplification system. One method of isolating target DNA is crude extraction which is useful for relatively large samples. Briefly,

mononuclear cells from samples of blood, amniocytes from amniotic fluid, cultured chorionic villus cells, or the like are isolated by layering on sterile Ficoll-Hypaque gradient by standard procedures. Interphase cells are collected and washed three times in sterile phosphate buffered saline before DNA extraction. If testing DNA from peripheral blood lymphocytes, an osmotic shock (treatment of the pellet for 10 sec with distilled water) is suggested, followed by two additional washings if residual red blood cells are visible following the initial washes. This will prevent the inhibitory effect of the heme group carried by hemoglobin on the PCR reaction. If PCR testing is not performed immediately after sample collection, aliquots of  $10^6$  cells can be pelleted in sterile Eppendorf tubes and the dry pellet frozen at  $-20^{\circ}\text{C}$  until use.

The cells are resuspended ( $10^6$  nucleated cells per  $100\ \mu\text{l}$ ) in a buffer of 50 mM Tris-HCl (pH 8.3), 50 mM KCl 1.5 mM  $\text{MgCl}_2$ , 0.5% Tween 20, 0.5% NP40 supplemented with  $100\ \mu\text{g/ml}$  of proteinase K. After incubating at  $56^{\circ}\text{C}$  for 2 hr. the cells are heated to  $95^{\circ}\text{C}$  for 10 min to inactivate the proteinase K and immediately moved to wet ice (snap-cool). If gross aggregates are present, another cycle of digestion in the same buffer should be undertaken. Ten  $\mu\text{l}$  of this extract is used for amplification.

When extracting DNA from tissues, e.g., chorionic villus cells or confluent cultured cells, the amount of the above mentioned buffer with proteinase K may vary according to the size of the tissue sample. The extract is incubated for 4-10 hrs at  $50^{\circ}$ - $60^{\circ}\text{C}$  and then at  $95^{\circ}\text{C}$  for 10 minutes to inactivate the proteinase. During longer incubations, fresh proteinase K should be added after about 4 hr at the original concentration.

When the sample contains a small number of cells, extraction may be accomplished by methods as described in Higuchi, "Simple and Rapid Preparation of Samples for PCR", in *PCR Technology*, Ehrlich, H.A. (ed.), Stockton Press, New York, which is incorporated herein by reference. PCR can be employed to amplify target regions in very small numbers of cells (1000-5000) derived from individual colonies from bone marrow and peripheral blood cultures. The cells in the sample are suspended in  $20\ \mu\text{l}$  of PCR lysis buffer (10 mM Tris-HCl (pH 8.3), 50 mM KCl, 2.5 mM  $\text{MgCl}_2$ , 0.1 mg/ml gelatin, 0.45% NP40, 0.45% Tween 20) and frozen until use. When PCR is to be performed,  $0.6\ \mu\text{l}$  of proteinase K (2 mg/ml) is added to the cells in the PCR lysis buffer. The sample is then heated to about

60°C and incubated for 1 hr. Digestion is stopped through inactivation of the proteinase K by heating the samples to 95°C for 10 min and then cooling on ice.

A relatively easy procedure for extracting DNA for PCR is a salting out procedure adapted from the method described by Miller et al., *Nucleic Acids Res.* 16:1215 (1988), which is incorporated herein by reference. Mononuclear cells are separated on a Ficoll-Hypaque gradient. The cells are resuspended in 3 ml of lysis buffer (10 mM Tris-HCl, 400 mM NaCl, 2 mM Na<sub>2</sub> EDTA, pH 8.2). Fifty µl of a 20 mg/ml solution of proteinase K and 150 µl of a 20% SDS solution are added to the cells and then incubated at 37°C overnight. Rocking the tubes during incubation will improve the digestion of the sample. If the proteinase K digestion is incomplete after overnight incubation (fragments are still visible), an additional 50 µl of the 20 mg/ml proteinase K solution is mixed in the solution and incubated for another night at 37°C on a gently rocking or rotating platform. Following adequate digestion, one ml of a 6M NaCl solution is added to the sample and vigorously mixed. The resulting solution is centrifuged for 15 minutes at 3000 rpm. The pellet contains the precipitated cellular proteins, while the supernatant contains the DNA. The supernatant is removed to a 15 ml tube that contains 4 ml of isopropanol. The contents of the tube are mixed gently until the water and the alcohol phases have mixed and a white DNA precipitate has formed. The DNA precipitate is removed and dipped in a solution of 70% ethanol and gently mixed. The DNA precipitate is removed from the ethanol and air-dried. The precipitate is placed in distilled water and dissolved.

Kits for the extraction of high-molecular weight DNA for PCR include a Genomic Isolation Kit A.S.A.P. (Boehringer Mannheim, Indianapolis, Ind.), Genomic DNA Isolation System (GIBCO BRL, Gaithersburg, Md.), Elu-Quik DNA Purification Kit (Schleicher & Schuell, Keene, N.H.), DNA Extraction Kit (Stratagene, LaJolla, Calif.), TurboGen Isolation Kit (Invitrogen, San Diego, Calif.), and the like. Use of these kits according to the manufacturer's instructions is generally acceptable for purification of DNA prior to practicing the methods of the present invention.

The concentration and purity of the extracted DNA can be determined by spectrophotometric analysis of the absorbance of a diluted aliquot at 260 nm and 280 nm. After extraction of the DNA, PCR amplification may proceed. The first step of each cycle of the PCR involves the separation of the nucleic acid duplex formed by the primer

extension. Once the strands are separated, the next step in PCR involves hybridizing the separated strands with primers that flank the target sequence. The primers are then extended to form complementary copies of the target strands. For successful PCR amplification, the primers are designed so that the position at which each primer hybridizes along a duplex sequence is such that an extension product synthesized from one primer, when separated from the template (complement), serves as a template for the extension of the other primer. The cycle of denaturation, hybridization, and extension is repeated as many times as necessary to obtain the desired amount of amplified nucleic acid.

In a particularly useful embodiment of PCR amplification, strand separation is achieved by heating the reaction to a sufficiently high temperature for a sufficient time to cause the denaturation of the duplex but not to cause an irreversible denaturation of the polymerase (see U.S. Pat. No. 4,965,188, incorporated herein by reference). Typical heat denaturation involves temperatures ranging from about 80°C to 105°C for times ranging from seconds to minutes. Strand separation, however, can be accomplished by any suitable denaturing method including physical, chemical, or enzymatic means. Strand separation may be induced by a helicase, for example, or an enzyme capable of exhibiting helicase activity. For example, the enzyme RecA has helicase activity in the presence of ATP. The reaction conditions suitable for strand separation by helicases are known in the art (see Kuhn Hoffman-Berling, 1978, *CSH-Quantitative Biology*, 43:63-67; and Radding, 1982, *Ann. Rev. Genetics* 16:405-436, each of which is incorporated herein by reference).

Template-dependent extension of primers in PCR is catalyzed by a polymerizing agent in the presence of adequate amounts of four deoxyribonucleotide triphosphates (typically dATP, dGTP, dCTP, and dTTP) in a reaction medium comprised of the appropriate salts, metal cations, and pH buffering systems. Suitable polymerizing agents are enzymes known to catalyze template-dependent DNA synthesis. In some cases, the target regions may encode at least a portion of a protein expressed by the cell. In this instance, mRNA may be used for amplification of the target region. Alternatively, PCR can be used to generate a cDNA library from RNA for further amplification, the initial template for primer extension is RNA. Polymerizing agents suitable for synthesizing a complementary, copy-DNA (cDNA) sequence from the RNA template are reverse transcriptase (RT), such as avian myeloblastosis virus RT, Moloney murine leukemia virus

RT, or *Thermus thermophilus* (Tth) DNA polymerase, a thermostable DNA polymerase with reverse transcriptase activity marketed by Perkin Elmer Cetus, Inc. Typically, the genomic RNA template is heat degraded during the first denaturation step after the initial reverse transcription step leaving only DNA template. Suitable polymerases for use with a DNA template include, for example, *E. coli* DNA polymerase I or its Klenow fragment, T4 DNA polymerase, Tth polymerase, and *Taq* polymerase, a heat-stable DNA polymerase isolated from *Thermus aquaticus* and commercially available from Perkin Elmer Cetus, Inc. The latter enzyme is widely used in the amplification and sequencing of nucleic acids. The reaction conditions for using *Taq* polymerase are known in the art and are described in Gelfand, 1989, PCR Technology, *supra*.

#### Allele Specific PCR

Allele-specific PCR differentiates between target regions differing in the presence of a polymorphism. PCR amplification primers are chosen which bind only to certain alleles of the target sequence. This method is described by Gibbs, *Nucleic Acid Res.* 17:12427-2448 (1989).

#### Allele Specific Oligonucleotide Screening Methods

Further diagnostic screening methods employ the allele-specific oligonucleotide (ASO) screening methods, as described by Saiki et al., *Nature* 324:163-166 (1986). Oligonucleotides with one or more base pair mismatches are generated for any particular allele. ASO screening methods detect mismatches between variant target genomic or PCR amplified DNA and non-mutant oligonucleotides, showing decreased binding of the oligonucleotide relative to a mutant oligonucleotide. Oligonucleotide probes can be designed that under low stringency will bind to both polymorphic forms of the allele, but which at high stringency, bind to the allele to which they correspond. Alternatively, stringency conditions can be devised in which an essentially binary response is obtained, i.e., an ASO corresponding to a variant form of the target gene will hybridize to that allele, and not to the wild-type allele.



#### Ligase Mediated Allele Detection Method

Target regions of the DNA of a test subject can be compared with target regions in unaffected and affected family members by ligase-mediated allele detection. See Landegren et al., *Science* 241:107-1080 (1988). Ligase may also be used to detect point mutations in the ligation amplification reaction described in Wu et al., *Genomics* 4:560-569 (1989). The ligation amplification reaction (LAR) utilizes amplification of specific DNA sequence using sequential rounds of template dependent ligation as described in Wu, *supra*, and Barany, *Proc. Nat. Acad. Sci.* 88:189-193 (1990).

#### 10 Denaturing Gradient Gel Electrophoresis

Amplification products generated using the polymerase chain reaction can be analyzed by the use of denaturing gradient gel electrophoresis. Different alleles can be identified based on the different sequence-dependent melting properties and electrophoretic migration of DNA in solution. DNA molecules melt in segments, termed melting domains, under conditions of increased temperature or denaturation. Each melting domain melts cooperatively at a distinct, base-specific melting temperature ( $T_m$ ). Melting domains are at least 20 base pairs in length, and may be up to several hundred base pairs in length.

Differentiation between alleles based on sequence specific melting domain differences can be assessed using polyacrylamide gel electrophoresis, as described in Chapter 7 of Erlich, ed., *PCR Technology*, Principles and Applications for DNA Amplification, W.H. Freeman and Co., New York (1992), the contents of which are hereby incorporated by reference.

Generally, a target region to be analyzed by denaturing gradient gel electrophoresis is amplified using PCR primers flanking the target region. The amplified PCR product is applied to a polyacrylamide gel with a linear denaturing gradient as described in Myers et al., *Meth. Enzymol.* 155:501-527 (1986), and Myers et al., in *Genomic Analysis, A Practical Approach*, K. Davies Ed. IRL Press Limited, Oxford, pp. 95-139 (1988), the contents of which are hereby incorporated by reference. The electrophoresis system is maintained at a temperature slightly below the  $T_m$  of the melting domains of the target sequences.

In an alternative method of denaturing gradient gel electrophoresis, the target sequences may be initially attached to a stretch of GC nucleotides, termed a GC clamp, as described in Chapter 7 of Erlich, *supra*. Preferably, at least 80% of the nucleotides in the GC clamp are either guanine or cytosine. Preferably, the GC clamp is at least 30 bases long. This method is particularly suited to target sequences with high  $T_m$ 's.

Generally, the target region is amplified by the polymerase chain reaction as described above. One of the oligonucleotide PCR primers carries at its 5' end, the GC clamp region, at least 30 bases of the GC rich sequence, which is incorporated into the 5' end of the target region during amplification. The resulting amplified target region is run on an electrophoresis gel under denaturing gradient conditions as described above. DNA fragments differing by a single base change will migrate through the gel to different positions, which may be visualized by ethidium bromide staining.

#### Temperature Gradient Gel Electrophoresis

Temperature gradient gel electrophoresis (TGGE) is based on the same underlying principles as denaturing gradient gel electrophoresis, except the denaturing gradient is produced by differences in temperature instead of differences in the concentration of a chemical denaturant. Standard TGGE utilizes an electrophoresis apparatus with a temperature gradient running along the electrophoresis path. As samples migrate through a gel with a uniform concentration of a chemical denaturant, they encounter increasing temperatures. An alternative method of TGGE, temporal temperature gradient gel electrophoresis (TTGE or tTGGE) uses a steadily increasing temperature of the entire electrophoresis gel to achieve the same result. As the samples migrate through the gel the temperature of the entire gel increases, leading the samples to encounter increasing temperature as they migrate through the gel. Preparation of samples, including PCR amplification with incorporation of a GC clamp, and visualization of products are the same as for denaturing gradient gel electrophoresis.

### Single-Strand Conformation Polymorphism Analysis

Target sequences or alleles at the IGF-1R locus can be differentiated using single-strand conformation polymorphism analysis, which identifies base differences by alteration in electrophoretic migration of single stranded PCR products, as described in Orita et al.,  
5 *Proc. Nat. Acad. Sci.* 85:2766-2770 (1989). Amplified PCR products can be generated as described above, and heated or otherwise denatured, to form single stranded amplification products. Single-stranded nucleic acids may refold or form secondary structures which are partially dependent on the base sequence. Thus, electrophoretic mobility of single-stranded amplification products can detect base-sequence difference between alleles or target  
10 sequences.

### Chemical or Enzymatic Cleavage of Mismatches

Differences between target sequences can also be detected by differential chemical cleavage of mismatched base pairs, as described in Grompe et al., *Am. J. Hum. Genet.*  
15 48:212-222 (1991). In another method, differences between target sequences can be detected by enzymatic cleavage of mismatched base pairs, as described in Nelson et al., *Nature Genetics* 4:11-18 (1993). Briefly, genetic material from an animal and an affected family member may be used to generate mismatch free heterohybrid DNA duplexes. As used herein, "heterohybrid" means a DNA duplex strand comprising one strand of DNA  
20 from one animal, and a second DNA strand from another animal, usually an animal differing in the phenotype for the trait of interest. Positive selection for heterohybrids free of mismatches allows determination of small insertions, deletions or other polymorphisms that may be associated with IGF-1R polymorphisms.

### 25 Non-gel Systems

Other possible techniques include non-gel systems such as TAQMAN™ (Perkin Elmer). In this system oligonucleotide PCR primers are designed that flank the mutation in question and allow PCR amplification of the region. A third oligonucleotide probe is then designed to hybridize to the region containing the base subject to change between different  
30 alleles of the gene. This probe is labeled with fluorescent dyes at both the 5' and 3' ends. These dyes are chosen such that while in this proximity to each other the fluorescence of

one of them is quenched by the other and cannot be detected. Extension by *Taq* DNA polymerase from the PCR primer positioned 5' on the template relative to the probe leads to the cleavage of the dye attached to the 5' end of the annealed probe through the 5' nuclease activity of the *Taq* DNA polymerase. This removes the quenching effect allowing  
5 detection of the fluorescence from the dye at the 3' end of the probe. The discrimination between different DNA sequences arises through the fact that if the hybridization of the probe to the template molecule is not complete, i.e., there is a mismatch of some form, the cleavage of the dye does not take place. Thus only if the nucleotide sequence of the oligonucleotide probe is completely complimentary to the template molecule to which it is  
10 bound will quenching be removed. A reaction mix can contain two different probe sequences each designed against different alleles that might be present thus allowing the detection of both alleles in one reaction.

Yet another technique includes an Invader Assay which includes isothermal amplification that relies on a catalytic release of fluorescence.

#### 15 Non-PCR Based DNA Diagnostics

The identification of a DNA sequence linked to IGF-1R can be made without an amplification step, based on polymorphisms including restriction fragment length polymorphisms in an animal and a family member. Hybridization probes are generally  
20 oligonucleotides which bind through complementary base pairing to all or part of a target nucleic acid. Probes typically bind target sequences lacking complete complementarity with the probe sequence depending on the stringency of the hybridization conditions. The probes are preferably labeled directly or indirectly, such that by assaying for the presence or absence of the probe, one can detect the presence or absence of the target sequence. Direct  
25 labeling methods include radioisotope labeling, such as with  $^{32}\text{P}$  or  $^{35}\text{S}$ . Indirect labeling methods include fluorescent tags, biotin complexes which may be bound to avidin or streptavidin, or peptide or protein tags. Visual detection methods include photoluminescents, Texas red, rhodamine and its derivatives, red leuco dye and 3,3',5,5'-tetramethylbenzidine (TMB), fluorescein, and its derivatives, dansyl, umbelliferone and the  
30 like or with horse radish peroxidase, alkaline phosphatase and the like.

Hybridization probes include any nucleotide sequence capable of hybridizing to the mouse chromosome where IGF-1R resides, and thus defining a genetic marker linked to IGF-1R, including a restriction fragment length polymorphism, a hypervariable region, repetitive element, or a variable number tandem repeat. Hybridization probes can be any gene or a suitable analog. Further suitable hybridization probes include exon fragments or portions of cDNAs or genes known to map to the relevant region of the chromosome.

Preferred tandem repeat hybridization probes for use according to the present invention are those that recognize a small number of fragments at a specific locus at high stringency hybridization conditions, or that recognize a larger number of fragments at that locus when the stringency conditions are lowered.

One or more additional restriction enzymes and/or probes and/or primers can be used. Additional enzymes, constructed probes, and primers can be determined by routine experimentation by those of ordinary skill in the art and are intended to be within the scope of the invention.

Although the methods described herein may be in terms of the use of a single restriction enzyme and a single set of primers, the methods are not so limited. One or more additional restriction enzymes and/or probes and/or primers can be used, if desired. Indeed in some situations it may be preferable to use combinations of markers giving specific haplotypes. Additional enzymes, constructed probes and primers can be determined through routine experimentation, combined with the teachings provided and incorporated herein. Stand alone software as well as web-based software are available that allows the user to identify other restriction mapping sites in the DNA sequence, e.g., <http://www.restrictionmapper.org/>.

According to the invention, polymorphisms in the IGF-1R gene have been identified which have been associated with reproductive longevity and/or sustained performance under stress. The presence or absence of the markers, in one embodiment may be assayed by PCR-RFLP analysis using the restriction endonucleases and amplification primers may be designed using analogous human, mouse, or other IGF-1R sequences due to high homology in the region surrounding the polymorphisms, or may be designed using known IGF-1R gene sequence data as exemplified in Genbank or even designed from sequences obtained from linkage data from closely surrounding genes based

upon the teachings and references herein. The sequences surrounding the polymorphism will facilitate the development of alternate PCR tests in which a primer of about 4-30 contiguous bases taken from the sequence immediately adjacent to the polymorphism is used in connection with a polymerase chain reaction to greatly amplify the region before treatment with the desired restriction enzyme. The primers need not be the exact complement; substantially equivalent sequences are acceptable. The design of primers for amplification by PCR is known to those of skill in the art and is discussed in detail in Ausubel (ed.), "Short Protocols in Molecular Biology, Fourth Edition" John Wiley and Sons 1999. The following is a brief description of primer design.

#### Primer Design Strategy

Increased use of polymerase chain reaction (PCR) methods has stimulated the development of many programs to aid in the design or selection of oligonucleotides used as primers for PCR. Four examples of such programs that are freely available via the Internet are: PRIMER by Mark Daly and Steve Lincoln of the Whitehead Institute (UNIX, VMS, DOS, and Macintosh), Oligonucleotide Selection Program (OSP) by Phil Green and LaDeana Hiller of Washington University in St. Louis (UNIX, VMS, DOS, and Macintosh), PGEN by Yoshi (DOS only), and Amplify by Bill Engels of the University of Wisconsin (Macintosh only). Generally these programs help in the design of PCR primers by searching for bits of known repeated-sequence elements and then optimizing the  $T_m$  by analyzing the length and GC content of a putative primer. Commercial software is also available and primer selection procedures are rapidly being included in most general sequence analysis packages.

#### Sequencing and PCR Primers

Designing oligonucleotides for use as either sequencing or PCR primers requires selection of an appropriate sequence that specifically recognizes the target, and then testing the sequence to eliminate the possibility that the oligonucleotide will have a stable secondary structure. Inverted repeats in the sequence can be identified using a repeat-identification or RNA-folding program such as those described above (see prediction of Nucleic Acid Structure). If a possible stem structure is observed, the sequence of the

primer can be shifted a few nucleotides in either direction to minimize the predicted secondary structure. The sequence of the oligonucleotide should also be compared with the sequences of both strands of the appropriate vector and insert DNA. Obviously, a sequencing primer should only have a single match to the target DNA. It is also advisable to exclude primers that have only a single mismatch with an undesired target DNA sequence. For PCR primers used to amplify genomic DNA, the primer sequence should be compared to the sequences in the GenBank database to determine if any significant matches occur. If the oligonucleotide sequence is present in any known DNA sequence or, more importantly, in any known repetitive elements, the primer sequence should be changed. Depending on the desired test conditions, the sequences of the primers should be designed to provide for both efficient and faithful replication of the target nucleic acid. Methods of PCR primer design are common and well known in the art. (Rychlik, W. (1993) In White, B. A. (ed.), *Methods in Molecular Biology*, Vol. 15, pages 31-39, *PCR Protocols: Current Methods and Applications*. Humana Press, Inc., Totowa, N.J.).

The methods and materials of the invention may be used as the basis to search for polymorphisms in the IGF-1R gene of species that are associated with reproductive longevity and sustained performance under stress. This would allow uses to genetically type individual animals by detecting genetic differences in those animals. For instance, a sample of mouse genomic DNA may be evaluated by reference to one or more controls to determine if a polymorphism in the IGF-1R gene is present. Preferably, RFLP analysis is performed with respect to the mouse IGF-1R gene, and the results are compared with a control. The control is the result of a RFLP analysis of the mouse IGF-1R gene of a different mouse where the polymorphism of the mouse IGF-1R gene is known. Similarly, the IGF-1R genotype of a mouse may be determined by obtaining a sample of its genomic DNA, conducting RFLP analysis of the IGF-1R gene in the DNA, and comparing the results with a control. Again, the control is the result of RFLP analysis of the IGF-1R gene of a different mouse. The results genetically type the mouse by specifying the polymorphism(s) in its IGF-1R genes. Finally, genetic differences among mice can be detected by obtaining samples of the genomic DNA from at least two mice, identifying the presence a polymorphism in the IGF-1R gene, and comparing the results.

Such assays are useful for identifying the genetic markers relating reproductive longevity and the ability to sustained stress factors such as lactation and pregnancy, as discussed above and for the general scientific analysis of mouse genotypes' and phenotypes'.

5        The examples and methods herein disclose certain genes which have been identified to have a polymorphism which is associated either positively or negatively with a beneficial trait that will have an effect on performance under stress in animals, such as cattle, birds, and aquatic species, such as shrimp carrying this polymorphism. The identification of the existence of a polymorphism within a gene is often made by a single  
10    base alternative that results in a restriction site in certain allelic forms. A certain allele, however, as demonstrated and discussed herein, may have a number of base changes associated with it that could be assayed for which are indicative of the same polymorphism (allele). Further, other genetic markers or genes may be linked to the polymorphisms disclosed herein so that assays may involve identification of other genes or gene fragments,  
15    but which ultimately rely upon genetic characterization of animals for the same polymorphism. Any assay which sorts and identifies animals based upon the allelic differences disclosed herein are intended to be included within the scope of this invention.

#### Linkage Analysis

20        Diagnostic screening may be performed for polymorphisms that are genetically linked to a phenotypic variant in IGF-1R activity or expression, particularly through the use of microsatellite markers or single nucleotide polymorphisms (SNP). The microsatellite or SNP polymorphism itself may not be phenotypically expressed, but is linked to sequences that result in altered activity or expression. Two polymorphic variants may be in linkage  
25    disequilibrium, i.e., where alleles show non-random associations between genes even though individual loci are in Hardy-Weinberg equilibrium.

Linkage analysis may be performed alone, or in combination with direct detection of phenotypically evident polymorphisms. The use of microsatellite markers for genotyping is well documented. For examples, see Mansfield et al. (1994) *Genomics*  
30    24:225-233; and Ziegler et al. (1992) *Genomics* 14:1026-1031. The use of SNPs for genotyping is illustrated in Underhill et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:196-200.



Genetic linkage maps show the relative locations of specific DNA markers along a chromosome. Any inherited physical or molecular characteristic that differs among animals and is easily detectable in the laboratory is a potential genetic marker. DNA sequence polymorphisms are useful markers because they are plentiful and easy to  
5 characterize precisely. Many such polymorphisms are located in non-coding regions and do not affect the phenotype of the organism, yet they are detectable at the DNA level and can be used as markers. Examples include restriction fragment length polymorphisms (RFLPs), which reflect sequence variations in DNA sites or differences in the length of the product, which can be cleaved by DNA restriction enzymes, microsatellite markers, which  
10 are short repeated sequences that vary in the number of repeated units, single nucleotide polymorphisms (SNPs), and the like.

The "linkage" aspect of the map is a measure of how frequently two markers are inherited together. The closer the markers are to each other physically, the less likely a recombination event will fall between and separate them. Recombination frequency thus  
15 provides an estimate of the distance between two markers. The value of the genetic map is that an inherited trait can be located on the map by following the inheritance of a DNA marker present in affected animals, but absent in unaffected animals, even though the molecular basis for the trait may not yet be understood.

SNPs are generally biallelic systems, that is, there are two alleles that a population  
20 may have for any particular marker. This means that the information content per SNP marker is relatively low when compared to microsatellite markers, which may have upwards of 10 alleles. SNPs also tend to be population-specific; a marker that is polymorphic in one population may not be very polymorphic in another. SNP markers offer a number of benefits that will make them an increasingly valuable tool. SNPs, found  
25 approximately every kilobase (see Wang et al. (1998) *Science* 280:1077-1082), offer the potential for generating high density genetic maps, which will be extremely useful for developing haplotyping systems for genes or regions of interest, and because of the nature of SNPs, they may in fact be the polymorphisms associated with the traits under study. The low mutation rate of SNPs also makes them excellent markers for studying complex  
30 genetic traits.

One of skill in the art, once a polymorphism has been identified and a correlation to a particular trait established, will understand that there are many ways to genotype animals for this polymorphism. The design of such alternative tests merely represents optimization of parameters known to those of skill in the art and is intended to be within the scope of this invention as fully described herein.

The following examples serve to better illustrate the invention described herein and are not intended to limit the invention in any way. Those skilled in the art will recognize that there are several different parameters which may be altered using routine experimentation and which are intended to be within the scope of this invention.

#### Example 1

Identify polymorphisms at the *daf-2* (Insulin-like growth factor-1 receptor) gene in lines of mice selected for reproductive longevity and evaluating this gene as putative candidates for DNA markers for reproductive longevity in livestock.

#### Materials and Methods

The mouse population: The original mouse population, which was established by Agriculture and Agri-Food Canada in Ottawa in 1965, was a cross between two strains of mice (P and Q). The P strain was a cross between three inbred lines (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) and the Q was Falconer's strain, which had a substantial heterogeneous background (Garnett and Falconer 1975). Ancestry of the Q strain goes back to 1948, with a large contribution from the 'J' strain (Falconer 1973). The 'J' strain was a heterogeneous population of mixed origin, which was made from crosses between Bateman's high-lactation line, Goodale's and MacArthur's large body weight selected lines, and four mutant stocks with the C57-BL inbred line as part of their ancestry (Brown and Falconer 1960). This population 'was about as close as one could get with laboratory mice to a natural random-bred population' (Brown and Falconer 1960). Several strains were derived from the J stock, including Falconer's control line (JC), an inbred line (JU), and a high litter size selected line (JH). The JC and JU lines constituted half of the ancestry of the Q strain. The other half was from crosses between Goodale's and MacArthur's large body weight selected lines (that had contributed to the J stock), MacArthur's small body weight selected line, JH, and a line that derived from the J stock and had been selected for high growth rate on a restricted diet (Falconer 1960). The four inbred lines and two of the lines that contributed to the Q strain (MacArthur's small body weight selected line (SM/J) and

Goodale's large body weight selected line (LG/J)), are currently maintained at the Jackson Laboratories, Bar Harbor, Maine. The contribution of so many strains to this colony, which is the only non-inbred mouse model in the world selected for reproductive longevity, was important for ensuring that the base population was heterozygous at many loci.

- 5 Prior to the implementation of the selection program for reproductive longevity, both the P and Q stocks were maintained by random mating for 23 generations (80 breeding pairs in P and 45 males and 90 females in Q) to achieve linkage equilibrium. Two lines from each of the P and Q strains were then established, each with 92 pairs of breeders. One line derived from each of the P and Q stocks was selected for nursing ability of the
- 10 mother, and the other for body weight of progeny at 42 days of age. After 21 generations of selection, these four lines were crossed, and the synthetic stock was maintained by random mating for 12 generations to allow it to approach linkage equilibrium. One control (C1) and two selected lines, with (SA1) and without (SU1) standardizing litter size to 8, were established in 1982 and have been continuously selected for reproductive longevity
- 15 since then (Nagai *et al.* 1995). Replications from each of the control and selected lines were established (C2, SA2, SU2) in 1993 using the existing lines (generation 18 of the SA1 and SU1 and generation 44 of the C1). Also, the high performing animals from the different selected lines were mated to generate a new line with a more diverse genetic background, and a sample from the control lines was used to generate a new control line.
- 20 In each of the selected lines, one male and one female were caged at about eight weeks of age, and each pair was maintained in the same cage continuously until the next generation was established, using progeny from the latest parities. In the control lines, progenies from the first parity were used as breeders. The control and selected lines were maintained with 42 and 30 breeding pairs, respectively, avoiding full-sib mating (Nagai *et al.* 1995).
- 25 Performance of the three original lines (SA1, SA2, C1) at generations 12 and 16 is reported by Nagai *et al.* (1995), and at generation 24 by Farid *et al.* (2002). The average number of days from mating to the last parturition in generation 12 was 236, 265 and 159 for lines SA1, SU1 and C1, respectively, showing that reproductive longevity was improved by 48% in the SA1 and 67% in the SU1. The corresponding values at generation 16 were 79% and
- 30 80%, and at generation 24 were 86% and 61% for the SA1 and SU1 lines, respectively. The number of parturitions during lifetime has not changed in the control line (5.34, 4.90,

5.30 at generations 12, 16 and 24, respectively), while the SA1 line showed a steady improvement: 8.63, 8.84 and 10.6 (61.6%, 80.4% and 100%). The corresponding values for the SU1 line were 79.9%, 93.0% and 83.0%.

- 5 **Source of DNA:** DNA was extracted from blood or tissue of 261 breeder males and females from the lines C1 (generation 69), C2 (generation 70), SA1 and SU1 (generation 24), and from one progeny from each of 153 families from lines C1, C2, SA1, SA2, SU1 and SU2. DNA samples from the four inbred lines that have contributed to the base population (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) were obtained from the Jackson
- 10 Laboratories, Bar Harbor, Maine.

- Laboratory procedures:** There are two sequences of the mouse insulin-like growth factor-1 receptor cDNA in Genbank (accession numbers AF056187 (SEQ ID NO:1) and XM\_133508 (SEQ ID NO:3)), and sequences of most of this gene's exons and introns
- 15 included in the clone RP23-378H21 (Genbank accession number AC101879) (SEQ ID NO:6). Several overlapping PCR primers were designed to cover the entire coding region of the IGF-1R gene and its 3' UTR using the Oligo 6.0 primer analysis software (Molecular Biology Insight, cascade, CO, USA). Information on a few of these primers which amplified polymorphic regions is shown in Table 1.

20

Table 1. Information on the primers used to amplify polymorphic segments of the IGF-1R gene in mice.

SEQ ID NO	Primer name	Sequence (5'-3')	Location	MgCl <sub>2</sub> (mM)	Anneal. temp. (°C)	Size, bp
8	PSEQDF	GGAGATCATCGGCAGCATCAAG	Exon 21	2.5	58.0	216or 204
9	PSEQDR	GCCATTCTCAGCCTTGTGTCC	Exon 21			
10	PSECAF	GCATGTGCTGGCAGTATAACC	Exon 21	1.5	58.5	634
11	PSECAR	CAGAGGCCCATGTCTAGTTAAG	3' UTR			
12	PSEQ16F	AGAGTGGCCATCAAGACGGTA	Exon 16	2.0	58.5	486
13	PSEQ16R	GGCCTCAGAGACCGGAGAT	Exon 17			

- PCR amplifications were performed in 50 µL volumes containing (final
- 25 concentration) 0.1% Tween 20, 1 x PCR buffer, 1.5-2.0 mM MgCl<sub>2</sub>, 0.2 mM each dNTP,

400 nM each primer, 2 units of *Taq* polymerase (Roche) and 100 ng template DNA. The thermal cycler was set at 95°C for 2 min followed by 34 cycles at 94°C for 1 min, 55-67°C (depending on the primer) for 1 min, 72°C for 1 min and a final 9 min extension at 72°C. Long fragments were amplified using PCR cocktails similar to those explained above, except using 0.35 mM of each dNTP and 2.5 units of Long-Range *Taq* polymerase (Roche). Thermal cycler was set at an initial 2 min denaturation at 95°C, followed by 10 cycles of 94°C for 10 sec, 55-67°C for 30 sec and 68°C for 10 min. The next 20 cycles consisted of 94°C for 10 sec, annealing at 55-67°C for 30 sec, elongation at 68°C for 10 min plus an additional 20 sec for each new cycle and a final 9 min extension at 68°C.

Genotyping for the 12 bp deletion in exon 21 was performed using the GenScan option of an ABI 377 automated DNA sequencer. Two primers flanking the deletion were designed. The Hex Amidite label was placed on the forward primer. Since the deletion was from 3896 to 3907, the PCR product was 216 bp in the wild type (4002-3786) or 204 bp for the deletion. The PCR cocktail contained 1.25 µL of a 10X buffer, 1.25 µL of a 25mM MgCl<sub>2</sub>, 1.0 µL of a 1.25 mM dNTPs, 5 pmol of each primer, 0.2 µL of a 5 U/µL Amplitaq gold polymerase, 25 ng of DNA and water to 12.5 µL total volume. Thermal cycler conditions were 95°C for 8 minutes initial denaturation, followed by 30 cycles of 95°C for 30 sec, 58°C for 30 sec, 72°C for 60 sec, and a final extension of 72°C for 30 minutes. PCR products were maintained at 6°C until processed. One µL of PCR products were loaded into the sequencer.

#### Data analysis:

Conformation of genotype frequencies to Hardy-Weinberg equilibrium was tested using the GENEPop computer package (<http://wbiomed.curtin.edu.au/genepop>) using the default options (1000 dememorisation, 100 batches and 1000 iterations). The program uses the Markov chain method to estimate the exact Hardy-Weinberg probability without bias (Guo and Thompson, 1992). The probability of rejecting H<sub>0</sub>, i.e., genotype frequencies are in Hardy-Weinberg equilibrium and the standard error of this estimate were computed. When standard errors were larger than 0.01, the data were re-analysed using a larger number of batches. This program does not perform any test when a locus is monomorphic or quasi monomorphic (two alleles, but one is represented only once).

Pairwise tests for homogeneity of allele and genotype frequency distributions were also performed using the GENEPOP computer package which follows the Raymond and Rousset (1995) method. The hypotheses tested were that allele and genotype distributions were independent of lines (no difference between lines). An unbiased estimate of the Fisher's exact test on contingency tables is performed using the Markov chain method (1000 dememorisation, 100 batches and 1000 iterations). The program computes the probability of being wrong when  $H_0$  is rejected. Rare alleles (frequency of less than 5%) were not pooled together prior to the above tests.  $F_{IS}$  statistics, as the measures of inbreeding within each line (Wright, 1943, 1978), were computed for each polymorphic site in every line using the GENEPOP computer program.

## Results

**Polymorphism:** A total of 4434 bp of the IGF-1R gene, consisting of exons 2, 3, 9, 10, 12, 13, 14, 15, 16, 17 and 21 (2344 bp) and introns 10, 12, 13, 14 and 16 (2090 bp) in five to seven individuals from each of the three main lines (C1, SA1, SU1) were sequenced. No polymorphism was detected in exons 2, 3, 9, 10, 12, 13, 14, 15, 16, 17 or in introns 10, 12, 13 and 14. The following polymorphic sites have been detected:

Site A: A 'G' to 'A' substitution (GGTC to GATC) was detected in intron 16 of the gene. The 486 bp PCR product, spanning exons 16 and 17 and intron 16, was cut into 454 and 32 bp fragments ( $A_1$  allele) by the enzyme *DpnII* ( $\uparrow$ GATC). This nucleotide substitution resulted in the creation of a new recognition site for this enzyme, which cleaved the 454 bp fragment into 328 and 125 bp fragments ( $A_2$  allele). In addition, sequence information revealed a 'G' nucleotide insertion in intron 16, 153 bp 5' to the above point mutation, but no restriction enzyme was found for discriminatory typing of this insertion.

Site B: An *HpaII* ( $C\uparrow$ CGG) polymorphism was detected as a result of an 'A' to 'G' substitution at position 3876 in exon 21 (CCAG to CCGG). The enzyme had one recognition site in the PCR product (373 and 261 bp fragments,  $B_1$  allele) and the nucleotide substitution resulted in an additional recognition site for the enzyme (373, 134 and 127 bp fragments,  $B_2$  allele). This is a silent mutation, as both CCA and CCG code for the amino acid proline. The marker for coping with pregnancy and lactation stress in mice

is the sequence containing the 'A' nucleotide at position 3876 of the mouse IGF-1R gene, identified by the 373/261 bp fragments (B<sub>1</sub> allele). Since the substitution is 20 base pairs upstream from the 12 base pair deletion, the 261 bp and 127 bp bands will shift by 12 base pairs when animals are homozygous or heterozygous for the deletion allele (D<sub>2</sub>). As is known in the art, however, restriction patterns are not exact determinants of the sizes of fragments and are only approximate.

Site D: Site D: A 12 bp deletion was detected 20 bp 3' to the site B in exon 21 (positions 3896-3907 of the IGF-1R gene cDNA, Genbank accession number AF056187, SEQ ID NO:1). This 12 bp fragment (tggagatggagc) (SEQ ID NO:20) appears twice in tandem (D<sub>1</sub> allele) in or only once (D<sub>2</sub> allele) in this region, resulting in the deletion of four amino acids (leucine, glutamic acid, methionine, and glutamic acid) from the IGF-1R protein. One IGF-1R sequence (Genbank accession number AF056187, SEQ ID NO:1) has two copies of this fragment while two others (Genbank accession numbers XM\_133508 (SEQ ID NO:3) and AC101879 (, SEQ ID NO:6) have one copy.

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Allele and genotype frequency distributions: Although sites A and B are approximately 22 kb apart, all 153 juveniles and 261 breeders had exactly the same genotypes at these two sites, constituting only two alleles (A<sub>1</sub> and A<sub>2</sub>). Replicate lines of juvenile mice were not different from the main lines for allele or genotype frequencies at site A. The frequency of A<sub>1</sub> allele in breeders from the SU1 line (0.84) was significantly greater than those in the other three lines (0.48, 0.62, 0.63, Tables 2 and 3). A similar pattern was observed in the juveniles, where frequencies of the A<sub>1</sub> allele in the SU1 and SU2 lines (0.83 and 0.89) were significantly greater than those in SA1 (0.55), SA2 (0.46), C1 (0.48) and C2 (0.61) lines (Tables 4 and 5). Frequencies of A<sub>1</sub> allele in the C1 line were similar in breeders and juveniles (0.48), and were smaller than those in the C2 line in breeders (0.67, P<0.01) and juveniles (0.61, NS). Frequency of A<sub>1</sub> allele in selected and control lines in which litter size was not standardized (SU1, SU2, C2) was greater than that in the lines in which litter size was standardized (SA1, SA2, C1) in both breeders and juveniles, suggesting that the A<sub>1</sub> allele was possibly selected for under high levels of maternal stress.

30 The frequency of the A<sub>1</sub>A<sub>1</sub> genotype in breeders from SU1 line (0.71) was significantly greater than in other lines, which ranged between 0.23 (C1) and 0.47 (C2)

(Tables 2 and 3). Juveniles from the SU1 and SU2 lines had greater frequencies of the  $A_1A_1$  genotype (0.75 and 0.77) and lower frequencies of the  $A_2A_2$  genotype (0.10 and 0.0) than the other four lines, in which the frequencies of  $A_1A_1$  ranged from 0.17 to 0.44 and frequencies of  $A_2A_2$  ranged from 0.22 to 0.26 (Tables 4 and 5). Differences in genotype frequencies between SU1 and SU2 and the other lines were all significant, except for SU1 and C2 that approached significance ( $P=0.079$ ). Genotype frequency distributions conformed to Hardy-Weinberg proportions in all the lines. All four inbred lines (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) had the  $A_1A_1$  genotype at site A and the  $B_1B_1$  genotype at site B, indicating that the  $A_2$  and  $B_2$  alleles must have been introduced into the base population by the Q-strain.

No  $D_2$  allele was detected in any of the control mice. The frequency of the  $D_2$  allele (deletion) ranged from 0.10 to 0.19 in the selected lines in the juveniles and breeders. The selected lines within breeder and juvenile groups had comparable allele and genotype frequencies at site D. All selected lines had significantly different allele and genotype frequency distributions compared with the control lines in which the  $D_1$  allele was fixed (Tables 6, 7, 8, 9). Replicate lines of juvenile mice were not different from the main lines for allele or genotype frequencies at site D. Genotype frequency distributions conformed to Hardy-Weinberg proportions in all the lines, except in juveniles from the SA1 line, which was deficient in heterozygotes ( $F_{IS}=+0.449$ , Table 4). High proportions of the  $D_2$  allele appeared in the heterozygous state (0.179 to 0.385), and low proportions (0.0 to 0.107) were in homozygous form in all the selected lines, which is expected from a population in Hardy-Weinberg equilibrium in which one allele has a low frequency. The C57BL/6J had the  $D_2D_2$  genotype, but the other three inbred lines had the  $D_1D_1$  genotype.

Only six of the 10 possible genotypes were present in the population when the joint distribution of A and D sites was considered (Tables 10, 12), indicating the presence of three of the four possible haplotypes ( $A_1D_1$ ,  $A_1D_2$ ,  $A_2D_1$ ). Haplotype and genotype frequency distributions were significantly different among all the lines within breeder and juvenile groups, except those between replicate lines (Tables 10, 11, 12, 13). Haplotype frequency differences between selected and control lines were largely due to the absence of the  $A_1D_2$  haplotype in the latter. Differences among non-replicate selected lines for haplotype frequency distributions were mainly the result of higher frequencies of  $A_1D_1$



(0.69 to 0.74) and lower frequencies of  $A_2D_1$  (0.12 to 0.18) in selected non-standardized lines compared with those in standardized selected lines, which had lower frequencies of  $A_1D_1$  (0.28 to 0.46) and higher frequencies of  $A_2D_1$  (0.38 to 0.52). Genotype frequencies conformed to Hardy-Weinberg proportions in all the lines in both breeders and juveniles, except in the SA1 line in juveniles, which was deficient in heterozygotes ( $F_{IS}=+0.341$ , Table 12). There was no difference between male and female breeders for allele or genotype frequencies at any of the sites (data not shown).

### Discussion

Similarities between the replicate lines for allele (haplotype) and genotype frequencies at all sites may indicate that the observed differences among non-replicate lines had happened before divergence of replicate lines from the main lines. These findings also imply that the size of the lines was great enough to make genetic drift a negligible force in changing the genetic profile of the lines in the last 8 generations of the selected lines (generations 18 to 24) and 26 generations of the controls (generations 44 to 69). The observed differences among the lines for allele frequency distributions can thus be largely attributed to the selection pressure applied to each line.

The finding that the  $A_1$  allele had a significantly greater frequency in breeder animals in which litter size was not standardized to 8 (selected and control lines) may suggest that although this gene has not been under selection pressure for reproductive longevity, the  $A_1$  allele may be linked to a QTL that has a favorable effect on maternal stress. Most female mice conceive while still nursing, which imposes a great pressure on them, and the effect will be more pronounced when litter size is large. It seems that the  $A_1$  allele is associated with animals that may be able to better cope with such a stress. This finding has some ramifications in the livestock industry, such as swine and dairy cattle, where lactation and pregnancy often coincide. This is the first evidence showing that such a characteristic is genetically controlled.

The results from site D provide a different picture than of site A. The absence of the  $D_2$  allele (deletion) in the control lines, and the similarity between all the selected lines for the allele and genotype frequencies within breeders and juveniles may suggest that the  $D_2$  allele (or an allele which is linked to  $D_2$ ) had a negative effect on early reproduction, and

has therefore been eliminated from the control lines. This conclusion is based on three notions. First, the frequency of the  $D_2$  allele in the original population was expected to be at least 0.125, because C57BL/6J with the  $D_2D_2$  genotype provided 1/8 of the genes to the original population, and this line had also contributed to the Q-strain. The effects of 21 generations of selection for nursing ability of the mother and body weight of progeny that was applied to the original population before the establishment of the base population for this experiment is not known. Assuming, however, that the frequency of the  $D_2$  allele was not drastically changed, it is unlikely that the  $D_2$  allele with such a frequency had not been included in the first generation of the control line merely by chance. Second, absence of the  $D_2$  allele in the control lines was not because of the small number of mice that were genotyped. The probability ( $\alpha$ ) that an allele with the frequency of  $Y$  or less in a population falls into a sample of size  $n$  (i.e.,  $2n$  alleles) is  $\log(1-\alpha) = 2n \log(1-Y)$ . Setting  $n=25$ , which was the smallest sample size of the control lines in juveniles, and  $Y=0.10$  (the smallest estimate of the  $D_2$  frequency in any line) will result in  $\alpha=0.994$ , i.e., there is at least 99% probability that the  $D_2$  allele with a frequency of 0.10 would be included in a sample of size 25. Combining the two control lines of juveniles will increase this probability to 99.99%. The total number of control mice tested (juveniles and breeders) was 217, suggesting that the  $D_2$  allele certainly does not exist in the control lines. Third, in the control lines, the male is removed from the cage 14 to 17 days following pairing. Replacement mice in the control lines are thus selected from females that conceived within the first 14 to 17 days after exposure to a male. The control lines, therefore, have been under mild selection for early reproduction. Although more studies are needed, it seems logical to believe that deletion of four amino acids from the IGF-1R would have some negative effect on the function of this polypeptide. The only explanation for the  $D_2$  allele to have a frequency of 0.10 to 0.20 in the selected lines is that this allele, or one which is linked to it, had a positive effect on reproduction at a later age. In addition, the  $D_2$  allele was largely in the heterozygous state, which will mask any negative effect of the allele.

The D and A sites are only 20 bp apart, and thus the likelihood of a crossing-over between them is very slim. Differences between lines for allele frequencies at sites A and D should be sought in the origin of the haplotypes. Since the only source of the  $A_2$  allele was the Q strain, and there was no  $A_2D_2$  haplotype in the population, it seems logical to assume

that the  $A_2D_1$  haplotype originated from the Q-strain and the  $A_1D_2$  haplotype originated from C57BL/6J (the only inbred line carrying the  $A_1D_2$  haplotype). Line C57BL/6J had a minor contribution to the Q strain, indicating that the Q strain might have carried the  $A_1D_2$  haplotype as well. The  $A_1D_1$  haplotype originated from the other three inbred lines as well  
5 as from the Q-strain. It seems reasonable to conclude that the  $A_1D_2$  haplotype, which originated from the C57BL/6J line and has been eliminated from the control lines, is a QTL with a negative effect on early reproduction and a positive effect on reproductive longevity. The  $A_2D_1$  haplotype that originated from the Q strain and had high frequencies in non-standardized lines (SU1, SU2, C2) may be a QTL that has been selected for under maternal  
10 pressure (large litter size, high milk production, pregnancy).

$F_{IS}$  is a measure of the inbreeding coefficient of individuals in a subdivided population due to nonrandom mating, or inbreeding of an individual relative to the sub-population to which it belongs (Wright, 1943, 1978; Nei, 1973; Hartl and Clark, 1989). When mating is at random in a sub-population,  $F_{IS}$  is equal to zero. Positive  $F_{IS}$  values  
15 indicate within sub-populations inbreeding (more homozygosity than expected) due to mating between relatives. Negative  $F_{IS}$  values show less homozygosity than expected from a population at Hardy-Weinberg equilibrium. Conformation of genotype frequency distributions to Hardy-Weinberg values and small  $F_{IS}$  estimates indicate that mating between animals with respect to sites A and D and their joint distribution has been at  
20 random in all the lines except SA1 in juveniles. This is expected in view of the fact that the effect of individual alleles on phenotype (reproductive longevity) has not been visible.

Many lines of mice contributed to the base population, making it a heterogeneous stock with many segregating loci upon which selection pressure has been applied for 24 generations. The fact that allele frequencies at sites A and D in the entire sample were 0.63  
25 and 0.89 in juveniles and 0.63 and 0.94 in breeders, respectively, point to the heterogeneity of the population at the present time. The observed genetic variability makes this colony unique.

Table 2. Distribution of allele and genotype frequencies at site A<sup>1</sup> at the IGF-1R locus in breeder mice, test for Hardy-Weinberg equilibrium and F<sub>IS</sub> estimates by line and sex.

Line	Sex	Allele frequency		Genotype frequency			No. of mice	H-W prob	F <sub>IS</sub>
		A <sub>1</sub>	A <sub>2</sub>	A <sub>1</sub> A <sub>1</sub>	A <sub>2</sub> A <sub>2</sub>	A <sub>1</sub> A <sub>2</sub>			
SA1 Selected (standardized)	F	0.648	0.352	0.407	0.111	0.481	27		
	M	0.603	0.397	0.379	0.172	0.448	29		
	Total	0.625	0.375	0.393	0.143	0.464	56	1.00	0.019
SU1 Selected (Non-standardized)	F	0.881	0.119	0.809	0.048	0.143	21		
	M	0.810	0.190	0.619	0.000	0.381	21		
	Total	0.845	0.155	0.714	0.024	0.262	42	1.00	0.011
C1 Control (standardized)	F	0.488	0.512	0.190	0.214	0.595	42		
	M	0.476	0.523	0.262	0.310	0.429	42		
	Total	0.482	0.518	0.226	0.262	0.512	84	1.00	-0.019
C2 Selected (non-standardized)	F	0.700	0.300	0.500	0.100	0.400	40		
	M	0.641	0.359	0.436	0.154	0.410	39		
	Total	0.671	0.329	0.468	0.127	0.405	79	0.45	0.089
Total		0.628	0.372	0.414	0.157	0.429	261	0.99	

1-Site A is a 'G' to 'A' substitution in intron 16, which is in linkage disequilibrium with an 'A' to 'G' substitution in exon 21 (site B).

5

Table 3. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site A in breeder mice.

Line	SA1	SU1	C1	C2
SA1	-	0.001	0.020	0.436
SU1	0.001	-	0.000	0.003
C1	0.020	0.000	-	0.002

C2	0.446	0.006	0.001	-
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Table 4. Distribution of allele and genotype frequencies at site A of the IGF-1R locus in juveniles, test for Hardy-Weinberg equilibrium and  $F_{IS}$  estimates by line.

Line		Allele frequency		Genotype frequency			No. of mice	H-W prob.	$F_{IS}$
		A <sub>1</sub>	A <sub>2</sub>	A <sub>1</sub> A <sub>1</sub>	A <sub>2</sub> A <sub>2</sub>	A <sub>1</sub> A <sub>2</sub>			
Selected (Standardized)	SA1	0.552	0.448	0.345	0.241	0.414	29	0.45	0.180
	SA2	0.458	0.542	0.167	0.250	0.583	24	0.68	-0.154
Selected (Non- standardized)	SU1	0.825	0.175	0.750	0.100	0.150	20	0.07	0.500
	SU2	0.885	0.115	0.769	0.000	0.231	26	1.00	-0.111
Control (standardized)	C1	0.481	0.519	0.222	0.259	0.519	27	1.00	-0.020
Control (non- standardized)	C2	0.611	0.389	0.444	0.222	0.333	27	0.13	0.316
Total		0.627	0.373	0.438	0.183	0.379	153	0.46	0.109

Table 5. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site A in juveniles.

Line	SA1	SA2	SU1	SU2	C1	C2
SA1	-	0.428	0.005	0.000	0.570	0.567
SA2	0.451	-	0.000	0.000	0.845	0.160
SU1	0.014	0.001	-	0.545	0.001	0.038
SU2	0.000	0.000	0.592	-	0.000	0.001
C1	0.588	0.836	0.002	0.000	-	0.246
C2	0.617	0.189	0.079	0.004	0.279	-

5 Table 6. Distribution of allele and genotype frequencies of the deletion<sup>1</sup> at the IGF-1R locus in breeder mice, test for Hardy-Weinberg equilibrium and  $F_{IS}$  estimates by line and sex.

Line	Sex	Allele frequency		Genotype frequency			H-W Prob	$F_{IS}$
		D <sub>1</sub>	D <sub>2</sub>	D <sub>1</sub> D <sub>1</sub>	D <sub>2</sub> D <sub>2</sub>	D <sub>1</sub> D <sub>2</sub>		
SA1 Selected (standardized)	F	0.796	0.204	0.593	0.000	0.407		
	M	0.862	0.138	0.758	0.034	0.207		
	Total	0.830	0.170	0.679	0.018	0.304	1.00	-0.069
SU1 Selected (Non-standardized)	F	0.929	0.071	0.857	0.000	0.143		
	M	0.857	0.143	0.714	0.000	0.286		
	Total	0.893	0.107	0.786	0.000	0.214	1.00	-0.108
C1 Control (standardized)	F	1.000	0.000	1.000	0.000	0.000		
	M	1.000	0.000	1.000	0.000	0.000		

	Total	1.000	0.000	1.000	0.000	0.000	-	-
C2 Selected (non- standardized)	F	1.000	0.000	1.000	0.000	0.000		
	M	1.000	0.000	1.000	0.000	0.000		
	Total	1.000	0.000	1.000	0.000	0.000	-	-
Total		0.946	0.054	0.897	0.003	0.100	1.00	

1-A 12 bp deletion ( $D_2$  allele) in exon 21 of the IGF-1R gene.

Table 7. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site D in breeder mice.

Line	SA1	SU1	C1	C2
SA1	-	0.305	0.000	0.000
SU1	0.218	-	0.000	0.000
C1	0.000	0.000	-	1.000
C2	0.000	0.000	1.000	-

5

Table 8. Distribution of allele and genotype frequencies of the deletion<sup>1</sup> at the IGF-1R locus (site D) in juveniles, test for Hardy-Weinberg equilibrium and  $F_{IS}$  estimates by line.

Line	Allele frequency		Genotype frequency			No. of mice	H-W prob.	$F_{IS}$
	$D_1$	$D_2$	$D_1D_1$	$D_2D_2$	$D_1D_2$			
SA1	0.804	0.196	0.714	0.107	0.179	28	0.04	0.449
SA2	0.804	0.196	0.652	0.044	0.304	23	1.00	0.055

SU1	0.900	0.100	0.800	0.000	0.200	20	1.00	-0.086
SU2	0.808	0.192	0.615	0.000	0.385	26	0.54	-0.220
C1	1.000	0.000	1.000	0.000	0.000	27	-	-
C2	1.000	0.000	1.000	0.000	0.000	25	-	-
	0.886	0.114	0.799	0.027	0.174	149	0.46	0.083

Table 9. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site D in juvenile mice.

Line	SA1	SA2	SU1	SU2	C1	C2
SA1	-	1.000	0.257	1.000	0.000	0.001
SA2	1.000	-	0.261	1.000	0.001	0.001
SU1	0.333	0.250	-	0.261	0.031	0.036
SU2	1.000	1.000	0.211	-	0.001	0.001
C1	0.005	0.001	0.029	0.000	-	1.000
C2	0.005	0.001	0.032	0.000	1.000	-

5 Table 10. Distribution of haplotype and genotype frequencies for the joint A and D sites in breeder mice, test for Hardy-Weinberg equilibrium and  $F_{IS}$  estimates by line and sex.

Line	Sex	Haplotype frequency	Genotype frequency	H-W	
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		A <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> D <sub>2</sub>	A <sub>2</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>1</sub> D <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>1</sub> D <sub>2</sub> D <sub>2</sub>	A <sub>1</sub> A <sub>1</sub> D <sub>1</sub> D <sub>2</sub>	A <sub>2</sub> A <sub>2</sub> D <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>2</sub> D <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>2</sub> D <sub>1</sub> D <sub>2</sub>	prob	F <sub>IS</sub>
SA1	F	0.444	0.204	0.352	0.185	0.000	0.222	0.111	0.296	0.185		
	M	0.466	0.138	0.396	0.172	0.034	0.172	0.172	0.414	0.034		
	Total	0.455	0.169	0.375	0.179	0.018	0.196	0.143	0.357	0.107	0.82	-0.051
SU1	F	0.810	0.071	0.119	0.667	0.000	0.143	0.047	0.143	0.000		
	M	0.667	0.143	0.190	0.429	0.000	0.190	0.000	0.286	0.095		
	Total	0.738	0.107	0.155	0.547	0.000	0.167	0.024	0.214	0.048	0.90	-0.009
C1	F	0.488	0.000	0.512	0.190	0.000	0.000	0.214	0.595	0.000		
	M	0.476	0.000	0.524	0.262	0.000	0.000	0.310	0.428	0.000		
	Total	0.482	0.000	0.518	0.226	0.000	0.000	0.262	0.512	0.000	1.00	-0.019
C2	F	0.700	0.000	0.300	0.500	0.000	0.000	0.100	0.500	0.000		
	M	0.641	0.000	0.357	0.436	0.000	0.000	0.154	0.410	0.000		
	Total	0.671	0.000	0.329	0.468	0.000	0.000	0.127	0.405	0.000	0.45	0.089
Total		0.575	0.054	0.371	0.341	0.004	0.069	0.157	0.399	0.031	0.98	

Table 11. Pairwise comparison of the lines for haplotype frequency (above diagonal) and genotype frequency (below diagonal) for joint A and D sites in breeder mice.

Line	SA1	SU1	C1	C2
SA1	-	0.000	0.000	0.000
SU1	0.000	-	0.000	0.000
C1	0.000	0.000	-	0.000
C2	0.000	0.000	0.001	-

Table 12. Distribution of haplotype and genotype frequencies for the joint A and D sites in juveniles, test for Hardy-Weinberg equilibrium and  $F_{IS}$  estimates by line.

Lines	Haplotype frequency			Genotype frequency						H-W prob.	$F_{IS}$
	A <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> D <sub>2</sub>	A <sub>2</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>1</sub> D <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>1</sub> D <sub>2</sub> D <sub>2</sub>	A <sub>1</sub> A <sub>1</sub> D <sub>1</sub> D <sub>2</sub>	A <sub>2</sub> A <sub>2</sub> D <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>2</sub> D <sub>1</sub> D <sub>1</sub>	A <sub>1</sub> A <sub>2</sub> D <sub>1</sub> D <sub>2</sub>		
SA1	0.357	0.196	0.446	0.21	0.11	0.00	0.25	0.25	0.14	0.04	0.341
SA2	0.283	0.196	0.522	0.09	0.00	0.00	0.22	0.35	0.26	0.63	-0.048
SU1	0.725	0.100	0.175	0.55	0.00	0.20	0.10	0.15	0.00	0.17	0.218
SU2	0.692	0.192	0.115	0.46	0.00	0.31	0.00	0.15	0.08	0.68	-0.125
C1	0.481	0.000	0.519	0.22	0.00	0.00	0.26	0.52	0.00	1.00	-0.022
C2	0.620	0.000	0.380	0.48	0.00	0.00	0.24	0.28	0.00	0.08	0.423
Total	0.520	0.114	0.366	0.33	0.00	0.09	0.18	0.29	0.08	0.16	0.135

5 Table 13. Pairwise comparison of the lines for haplotype frequency (above diagonal) and genotype frequency (below diagonal) for joint A and D sites in juveniles.

Line	SA1	SA2	SU1	SU2	C1	C2
SA1	-	0.696	0.001	0.000	0.001	0.001
SA2	0.749	-	0.000	0.000	0.001	0.000
SU1	0.008	0.001	-	0.415	0.000	0.010

SU2	0.001	0.000	0.442	-	0.000	0.000
C1	0.005	0.001	0.000	0.000	-	0.171
C2	0.003	0.000	0.018	0.000	0.217	-

### Example 2

#### Identification of Polymorphisms in the IGF-1R Gene in a Line of Pigs for the Development of DNA

5

Animals from a single commercial operation were used to find polymorphisms in candidate genes for reproductive longevity in pigs. Sourcing all animals from a single farm should ensure a similar environment for both high and low reproductive longevity groups. Five living sows with very high parity numbers were chosen as representing high reproductive longevity and five animals culled for reproductive reasons at low parity numbers were chosen as representing low reproductive longevity.

10

DNA was extracted from tissue samples from these 10 animals and the DNA used to amplify regions of candidate genes using PCR. PCR primers were designed from pig DNA sequence, or from exonic sequence of the homologous gene in other species such as mouse or human. The DNA sequence of these PCR products was then determined and the sequences compared to identify any polymorphisms. Each polymorphism was then assayed over a larger sample of animals from the same commercial population to look for evidence of association with increased reproductive longevity.

15

Five polymorphisms were found. Of these five, 2 were in intron 16 (SNP16i27 and SNP16i73); one in exon 8 (SNP1772); one in exon 16 (SNP3085); and one in exon 21 (SNP3757).

20

The polymorphism designated SNP1772, was characterized as a G/A SNP. It is a *TaqI* RFLP. Polymorphism SNP16i27 (position 27 from the end of exon 16) is a G/A SNP. It is an *AvaII* RFLP. SNP16i73 (position 73 from the end of exon 16) is a G/C SNP. It is a *MnlI* RFLP.

25

### PCR-RFLP Protocol for SNP16i27

Primers used in RLFP analysis were as follow:

Primer 16 5' – CCT CCG TGA TGA AGG AGT TC – 3' (SEQ ID NO:14)

5 Primer 17 5' – TCA GTT CCA TGA TGA CCA GC – 3' (SEQ ID NO:15)

PCR was carried out using the following conditions:

	10X PCR Buffer	1.0 ul
	2mM dNTPs	1.0 ul
10	25mM MgCl <sub>2</sub>	1.0 ul
	5uM Primer 16	1.0 ul
	5uM Primer 17	1.0 ul
	Amplitaq Gold	0.1 ul
	QH <sub>2</sub> O	3.9 ul
15	DNA	1.0 ul

Thermal Cycling conditions on the PE9700 were as follow:

94°C – 12 min

20 94°C – 30 sec

58°C – 30 sec

72°C – 30 sec

(repeated for 39 additional cycles)

25 72°C – 7 min

4°C – hold

Digested with *Ava*II restriction endonuclease.

30 The expected product sizes were: allele 1: 141, 122, 44; allele 2: 122, 81, 60, 44.

### PCR-RFLP Protocol for SNP16i73

35 Primers used in RLFP analysis were as follow:

Primer 16 5' – CCT CCG TGA TGA AGG AGT TC – 3' (SEQ ID NO:16)

Primer 17 5' – TCA GTT CCA TGA TGA CCA GC – 3' (SEQ ID NO:17)

PCR was carried out using the following conditions:

40	10X PCR Buffer	1.0 ul
	2mM dNTPs	1.0 ul
	25mM MgCl <sub>2</sub>	1.0 ul
	5uM Primer 16	1.0 ul
	5uM Primer 17	1.0 ul
45	Amplitaq Gold	0.1 ul
	QH <sub>2</sub> O	3.9 ul
	DNA	1.0 ul

Thermal Cycling conditions on the PE9700

94°C – 12 min

- 5    94°C – 30 sec  
      58°C – 30 sec  
      72°C – 30 sec  
      (repeat for 39 additional cycles)

- 10   72°C – 7 min  
      4°C – hold

Digested with *MnII* restriction endonuclease.

- 15   The expected product sizes were: allele 1: 241, 55, 11; allele 2: 137, 104, 55, 11.

PCR-RFLP Protocol for SNP1772

- 20   Primers used in RLFP analysis were as follow:

Primer 9 5' – GGA GTA TGA TGG GCA GGA T – 3' (SEQ ID NO:18)

Primer 8 5' – GAA GCA TTG GTG CGA ATG TA – 3' (SEQ ID NO:19)

PCR was carried out using the following conditions:

- |    |                        |        |
|----|------------------------|--------|
| 25 | 10X PCR Buffer         | 1.0 ul |
|    | 2mM dNTPs              | 1.0 ul |
|    | 25mM MgCl <sub>2</sub> | 0.6 ul |
|    | 5uM Primer 9           | 1.0 ul |
|    | 5uM Primer 8           | 1.0 ul |
| 30 | Amplitaq Gold          | 0.1 ul |
|    | QH <sub>2</sub> O      | 4.3 ul |
|    | DNA                    | 1.0 ul |

Thermal Cycling conditions on the PE9700

- 35   94°C – 12 min

      94°C – 30 sec

      56°C – 30 sec

      72°C – 30 sec

- 40   (repeat for 39 additional cycles)

      72°C – 7 min

      4°C – hold

Digested with *TaqI* restriction endonuclease.

- 45

The expected product sizes were: allele 1: 219; allele 2: 135, 84.

### Example 3 SNP 3832

Samples from old surviving sows and from young sows culled during the first 4

5 parities.

996 sows from four different farms were genotyped and tested for the effect of SNP 3832 on the number of parities. Allele "2" was found to be positively associated with longevity. In average sows of the 22, 12 and 11 genotypes were culled after 7.4, 6.7 and 5.1 parities, respectively. The additive effect of SNP 3832 was estimated to be 1.11/parities/allele ( $P=0.004$ ) with no dominance effect. The effect is significant, but over estimated due to the data structure.

Germany (GER): Longevity (reproduction) data from sows with known pedigree with DNA samples from their sires.

Data of over 19,000 sows, daughters of 179 sires were used in the analysis. Each sire had at least 50 daughters. There are 76 litter farms represented and the litters were from 1996 to 2001. Phenotypic performance of each sire was estimated based on the daughters' performances, and genotypic data was collected for the sires. Allele "2" found to be positively associated with longevity. SNP 3832 estimated additive effect represent a contrast between homozygous sows of 38 days to culling ( $P=0.062$ ).

20 A large number of animals were genotyped for the SNP 3832 marker. Animals carrying two copies of the "2" allele (homozygous) are expected to produce more parities and stay in the herd longer.

#### PCR for SNP 3832

25 Primer 22 5' - AAG ATG AGG CCT TCC TT - 3' (SEQ ID NO:21)  
Primer 23 5' - GAT CAG CAG GTC GAG GAC TG - 3' (SEQ ID NO:22)

#### PCR Conditions:

10X PCR Buffer	1.0 ul
30 2mM dNTPs	1.0 ul
25mM MgCl <sub>2</sub>	0.6 ul
5uM Primer 22	1.0 ul
5uM Primer 23	1.0 ul
Amplitaq Gold	seem to 0.1 ul
35 QH <sub>2</sub> O	4.3 ul
DNA	1.0 ul

Thermal Cycling conditions on the PE9700

94°C - 12 min

- 5    94°C - 30 sec  
     58°C - 30 sec  
     72°C - 1 min  
     (repeat for 34 additional cycles)

- 10   72°C - 7 min  
     4°C - hold

Digest with *FokI*

- 15   Expected product sizes: allele 1: 347; allele 2: 292, 55.

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What is claimed is:

1. A method for genetically identifying an animal with respect to its potential to reproductive longevity comprising:  
obtaining a sample of genetic material from an animal; and  
5 assaying for the presence of a polymorphism in the insulin-like growth factor 1 receptor gene (IGF-1R), wherein the polymorphism is associated with reproductive longevity.
2. The method of claim 1 wherein said polymorphism is selected from the group  
10 consisting of: a single nucleotide polymorphism (SNP), a deletion, and an insertion.
3. The method of claim 1 wherein the animal is selected from a group consisting of: a mouse, a pig, and a cow.
- 15 4. The method of claim 1 wherein a step of assaying the polymorphism is selected from the group consisting of: direct sequencing, restriction fragment length polymorphism (RFLP) analysis, single-stranded conformation polymorphism (SSCP), PCR amplification of specific alleles, amplification of DNA target by PCR followed by a mini-sequencing assay, allelic discrimination during PCR, Genetic Bit Analysis, Pyrosequencing,  
20 oligonucleotide ligation assay, and analysis of melting curves.
5. The method of claim 4 wherein the step of assaying the polymorphism is RFLP.
6. The method of claim 4 wherein the step of assaying the polymorphism is SSCP.
- 25 7. The method of claim 1 wherein the step of assaying for the presence of the polymorphism comprises the steps of:  
digesting the genetic material with a restriction endonuclease that cleaves the gene in at  
least one place, wherein a particular restriction endonuclease pattern indicates the  
30 presence or absence of a polymorphism;  
separating the fragments obtained from the digestion;

detecting a restriction pattern generated by the fragments; and  
comparing the pattern with a second restriction pattern for the gene obtained by using the  
restriction endonuclease, wherein the second restriction pattern is associated with  
reproductive longevity.

5

8. The method of claim 7 wherein said separation is by gel electrophoresis.

9. The method of claim 7 further comprising:

amplifying the gene or a portion thereof which contains at least one polymorphism, prior to

10 digestion.

10. The method of claim 9 wherein the amplification includes selecting a forward and a  
reverse sequence primer capable of amplifying a region of the gene which contains a  
polymorphism.

15

11. The method of claim 1 wherein the polymorphism is identified as an A to G  
nucleotide substitution at position 3876 of the gene.

12. The method of claim 1 wherein the polymorphism is identified as a G to A

20 nucleotide substitution at position 331 of the gene.

13. The method of claim 1 wherein the polymorphism is a 12 base pair deletion at  
positions 3896-3907 of the gene.

25 14. The method of claim 7 wherein the restriction endonuclease is *HpaII*.

15. The method of claim 7 wherein the restriction endonuclease is *DpnII*.

16. The method of claim 7 wherein the restriction endonuclease is *TaqI*.

30

17. The method of claim 7 wherein the restriction endonuclease is *MnII*.

18. The method of claim 7 wherein the restriction endonuclease is *Avall*.

19. The method of claim 10 wherein the forward primer is SEQ ID NO:8 and wherein  
5 the reverse primer is SEQ ID NO:9.

20. The method of claim 10 wherein the forward primer is SEQ ID NO:10 and wherein  
the reverse primer is SEQ ID NO:11.

10 21. The method of claim 10 wherein the forward primer is SEQ ID NO:12 and wherein  
the reverse primer is SEQ ID NO:13.

22. The method of claim 10 wherein the forward primer is SEQ ID NO:14 and wherein  
the reverse primer is SEQ ID NO:15.

15

23. The method of claim 10 wherein the forward primer is SEQ ID NO:16 and wherein  
the reverse primer is SEQ ID NO:17.

24. The method of claim 10 wherein the forward primer is SEQ ID NO:18 and wherein  
20 the reverse primer is SEQ ID NO:19.

25. A method of screening animals to determine those more likely to have reproductive  
longevity, the method comprising:

obtaining a biological sample from an animal; and

25 assaying for the presence of a genotype in the IGF-1R gene, wherein the genotype is  
associated with reproductive longevity and characterized by a restriction fragment  
pattern, wherein said pattern when compared to a second restriction pattern is  
known to have or not have a desired polymorphic marker, the presence of said  
marker being indicative of an animal more likely to have reproductive longevity.

30



26. The method of claim 25 wherein the assaying step comprises amplifying the gene or a region thereof containing the marker with a forward and a reverse sequence primer.

27. The method of claim 26 wherein the forward primer is SEQ ID NO:8 and the reverse primer is SEQ ID NO:9.

28. The method of claim 26 wherein the forward primer is SEQ ID NO:10 and the reverse primer is SEQ ID NO:11.

29. The method of claim 26 wherein the forward primer is SEQ ID NO:12 and said reverse primer is SEQ ID NO:13.

30. The method of claim 26 wherein the forward primer is SEQ ID NO:14 and the reverse primer is SEQ ID NO:15.

31. The method of claim 26 wherein the forward primer is SEQ ID NO:16 and the reverse primer is SEQ ID NO:17.

32. The method of claim 26 wherein the forward primer is SEQ ID NO:18 and the reverse primer is SEQ ID NO:19.

33. The method of claim 25 wherein the marker is *DpnII*.

34. The method of claim 25 wherein the marker is *HpaII*.

35. The method of claim 25 wherein the marker is *TaqI*.

36. The method of claim 25 wherein the marker is *MnII*.

37. The method of claim 25 wherein the marker is *AvaII*.

38. The method of claim 33 wherein a G to A nucleotide substitution results in a restriction pattern characterized by a 328 nucleotide fragment, a 125 nucleotide fragment, and a 32 nucleotide fragment.

5 39. The method of claim 34 wherein an A to G nucleotide substitution results in a restriction pattern characterized by a 373 nucleotide fragment, a 134 nucleotide fragment, and a 127 nucleotide fragment.

40. The method of claim 34 wherein the deletion is characterized by a 12 bp fragment  
10 having SEQ ID NO:20 appearing once in the IGF-1R gene.

41. The method of claim 35 wherein a G to A nucleotide substitution results in a restriction pattern characterized by a 135 nucleotide fragment and an 84 nucleotide fragment.

15 42. The method of claim 36 wherein an G to C nucleotide substitution results in a restriction pattern characterized by a 137 nucleotide fragment, a 104 nucleotide fragment, a 55 nucleotide fragment, and an 11 nucleotide fragment.

20 43. The method of claim 37 wherein an G to A nucleotide substitution results in a restriction pattern characterized by a 122 nucleotide fragment, an 81 nucleotide fragment, a 60 nucleotide fragment, and a 44 nucleotide fragment.

44. The method of claim 25 wherein said animal is selected from the group consisting  
25 of: a pig and a mouse.

45. A method for screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity, said method comprising:  
obtaining a genetic sample from an animal; and  
30 detecting the presence or absence of at least one allele in the IGF-1R gene wherein the presence of the allele is predictive of the animal having reproductive longevity.

46. The method of claim 45 wherein the allele is defined in intron 16 of the gene.

47. The method of claim 45 wherein the allele is defined in exon 21 at position 3876 of the gene.

5

48. The method of claim 45 wherein the allele is defined in exon 21 at positions 3896-3907 of the gene.

49. The method of claim 45 wherein the allele is defined at position 27 at the end of intron 16 of the gene.

10

50. The method of claim 45 wherein the allele is defined at position 73 at the end of intron 16 of the gene.

51. The method of claim 45 wherein the animal is selected from a group consisting of: a pig and a mouse.

15

52. A method for determining the haplotype of the IGF-1R gene of an animal comprising:

20

obtaining a genetic sample from an animal; and  
analyzing the genetic sample for the presence of an IGF-1R gene  $A_1D_1$ ,  $A_1D_2$ , or  $A_2D_1$  haplotype allele, wherein the haplotype effects reproductive performance or the ability to sustain stress factors.

53. The method of claim 52 wherein the  $A_1D_1$  allele is indicative of having a favorable effect on lactation and pregnancy stress.

25

54. The method of claim 52 wherein the  $A_1D_2$  allele is indicative of having a negative effect on reproductive performance.

30

55. The method of claim 52 wherein the A<sub>2</sub>D<sub>1</sub> allele is indicative of reproductive longevity.

56. The method of claim 52 wherein the animal is a mouse.

5

57. A method for genotyping an animal for reproductive longevity, the method comprising:

obtaining a sample of genetic material from an animal;

detecting a polymorphism in the IGF-1R gene of the animal;

10 determining whether the animal possesses a marker, wherein the marker is indicative of the animal having two copies of allele 2.

58. The method of claim 57 wherein the step of detecting the polymorphism comprises: digesting amplified nucleic acid with a restriction enzyme; and

15 separating the nucleic acid fragments according to size such that a restriction fragment pattern is generated,

wherein the restriction fragment pattern generated is indicative of an animal reproductive longevity.

20 59. The method of claim 57 wherein prior to digesting the nucleic acid with a restriction enzyme, amplifying the nucleic acid with a forward primer and a reverse primer.

60. The method of claim 59 wherein the forward and reverse primer is SEQ ID NO:21 and SEQ ID NO:22.

25

61. The method of claim 57 wherein the restriction enzyme is *FokI*.

62. The method of claim 58 wherein the restriction pattern characterized by a 295 nucleotide fragment, and a 55 nucleotide fragment.

30

63. The method of claim 57 wherein the marker is positively associated with longevity.

64. The method of claim 57 wherein the animal is a pig.

65. A method for genetically identifying an animal comprising:

obtaining a sample of genetic material from an animal; and

5 assaying for the presence of a genotype in the IGF-1R gene sequence as set forth in SEQ

ID NO:1 or a region thereof in the sample,

wherein the animal possesses a nucleic acid sequence having at least 95% sequence

identity to SEQ ID NO:1 or a fragment thereof.

10 66. The method of claim 65 wherein the polymorphism is identified by a G to A  
nucleotide substitution in intron 16.

67. The method of claim 65 wherein the polymorphism is identified by an A to G  
nucleotide substitution in exon 21.

15

68. The method of claim 65 wherein the polymorphism is identified as a 12 bp deletion  
in exon 21.

69. The method of claim 65 wherein the polymorphism is identified as an insertion of a  
20 G nucleotide in intron 16 at position 176.

70. The method of claim 65 wherein the animal is a mouse.

71. A method for genetically identifying an animal comprising:

25 obtaining a sample of genetic material from an animal; and

assaying for the presence of a genotype in the IGF-1R gene sequence as set forth in SEQ

ID NO:7 or a region thereof in the sample,

wherein the animal possesses a nucleic acid sequence having at least 95% sequence

identity to SEQ ID NO:7 or a fragment thereof.

30

72. The method of claim 71 wherein said polymorphism is identified as a G to A nucleotide substitution in intron 16.

73. The method of claim 71 wherein said polymorphism is identified as a G to C  
5 nucleotide substitution in intron 16.

74. The method of claim 71 wherein said polymorphism is identified as a G to A nucleotide substitution in exon 8.

10 75. The method of claim 71 wherein the animal is a pig.

76. The method of claim 65 wherein the polymorphism is an A to G nucleotide substitution in exon 21 at position 3876.

15 77. The method of claim 65 wherein the polymorphism is a 12 bp deletion in exon 21 at positions 3896-3907.

78. The method of claim 71 wherein said polymorphism is a G to A nucleotide substitution at position 27 from the end of intron 16.

20

79. The method of claim 71 wherein said polymorphism is a G to C nucleotide substitution at position 73 from the end of intron 16.

80. A method for genetically identifying cattle with respect to its potential to  
25 reproductive longevity comprising:  
obtaining a sample of genetic material from a cow; and  
assaying for the presence of a polymorphism in the insulin-like growth factor 1 receptor gene (IGF-1R), wherein the polymorphism is associated with reproductive longevity.

## ABSTRACT OF THE DISCLOSURE

Disclosed herein are embodiments for genotyping an animal for the presence of polymorphic alleles in the IGF-1R gene that are associated with reproductive longevity and/or ability to better sustain stress, and preferably selecting those animals for future breeding purposes.

5

## **Application Data Sheet**

### **Application Information**

Application Type::	Regular
Subject Matter::	Utility
Sequence submission?::	Yes
Computer Readable Form (CRF)?::	Yes
Number of copies of CRF::	1
Title:	INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) POLYMORPHIC ALLELES AND USE OF THE SAME TO IDENTIFY DNA MARKERS FOR REPRODUCTIVE LONGEVITY
Attorney Docket Number::	P05562US00
Request for Early Publication::	No
Request for Non-Publication::	No
Total Drawing Sheets::	83
Small Entity?::	No
Petition included?::	No

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City of mailing address::

State or Province of

mailing address::

Country of mailing address::

Postal or Zip Code of

mailing address::

1 atgaagtctg gctccggagg aggggtccccg acdctcgtgt gggggctcgt gttttctctcc  
61 gccgcgctct ctctctggcc gacgagtggg gaaatctgtg ggcccggcat tgacatccgc  
121 aacgactatc agcagctgaa ggccttgga aactgcacgg tgatcgaggg ctctctccac  
181 atcctgtctca tctccaaggc cgaggactac cgaagctacc gcttcccca gctcaccgtc  
241 atcactgagt acttgctgct ctcccgagtc gctggcctcg agagcctggg agacctcttc  
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361 gagatgacca atctcaagga tattgggctt tataatctga ggaacattac tcgggggggccc  
421 atcaggattg agaagaacgc cgacctctgt tacctctcca ccatagactg gtctctcatc  
481 ttggatgcgg tgtccaataa ctacattgtg gggaacaagc ccccgaagga atgtgggggac  
541 ctgtgtccag ggacattgga ggagaagccc atgtgtgaga agaccaccat caacaatgag  
601 tacaactacc gctgtggag cacaatctgc tgccagaaaa tgtgcccagg tgtgtcgggg  
661 aagcagacct gcaccgagaa caacgagtgc tgccacccgg agtgccctggg cagctgccac  
721 acaccggacg acaacacaaac ctgctgtggc tgccagacact actactacaa aggcgtgtgt  
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841 ttctgcgcca acatcccaa cgctgagagc agtgactcgg atggcttcgt tatccacgac  
901 gatgagtga tgcaggagt tccctcaggc ttcacccgca acagcaccca gagcatgtac  
961 tgtatccctt gcgaaggccc ctgccccaaa gtctgcggcg atgaagagaa gaaaacgaaa  
1021 accatcgatt cgggtgactt tgcctcaaat ctccaaggat gcaccatcct gaaggcgaaat  
1081 ctgcttatta accatccggg aggcaataac attgcctcgg agttggagaa cttcatgggg  
1141 ctcatcgagg tggtagaccg ctacgtgaag atccgccatt ctcatgcctt ggtctccttg  
1201 tccttctctga agaaccttcg tctcatctta ggagaggagc agctggaagg gaactactcc  
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1321 accgtcaggt ccggaagat gtactttgct ttcaatccca agctgtgtgt ctccgaaatt  
1381 taccgcatgg aggaagtga cggaaaccaag ggacgccaga gcaaagggga cataaacacc  
1441 aggaacaacg gagagcgagc ttcctgtgaa agtgatgttc tccgtttcac ctccaccag  
1501 acctggaaga accgaatcat cataacgtgg caccggtacc ggccgcccga ctaccgggat  
1561 ctcatcagct tcacagttaa ctacaaggag gcaccattta aaaacgttac ggaatatgac  
1621 gggcaggatg cctgtggctc caacagctgg aacatgggtg atgtagacct gcctccgaac  
1681 aaggaggggc agcctggcat tttactgcat gggctgaagc cctggaccca gtatgtgtc  
1741 tatgtcaagg ctgtgacct caccatgggt gaaaacgacc atatccgtgg ggccaaaagt  
1801 gaaatcttgt acattcgac caatgcttca gtcccttcca tccccctaga tgtcctctca  
1861 gcatcaaact ctctctctca gctgattgtg aagtggaaac ctccaactct gcccaatggg  
1921 aacttgagtt actacattgt gagggtggcg cggcagcccc aggatgggta cctgtaccgg  
1981 cacaactact gctccaaaga caaaataccc atcagaaagt acgccgatgg taccatcgac  
2041 gtggaggagg tgacggaaaa tcccaagaca gaagtgtgtg gtgggtgataa agggccatgc  
2101 tgcgcttgcc ctaaaactga agctgagaag caggctgaga aggaggaggc tgagtaccgt  
2161 aaagtctttg agaatttcct tcacaattcc atctttgtgc ccaggcccga aaggaggcgg  
2221 agagacgtca tgcaagtggc caacacgacc atgtccagcc gaagcaggaa caccacggta  
2281 gctgacacct acaatatcac agaccggag gagttcgaga cagagtacc tttctttgag  
2341 agcagagtgg ataacaagga gaggactgtc atctccaacc tccggccttt cactctgtac  
2401 cgcacgata tccacagctg caaccacgag gctgagaagc tgggctgcag cgctccaac  
2461 ttcgtctttg cgagaaccat gccagcagaa ggagcagatg atatccctgg tccggtgacc  
2521 tgggagccaa gaccgaaaa ctccatcttt ttaaagtggc cagaacccga gaaccccaac  
2581 ggattgatcc taatgtatga aattaaatac gggtcgcaag tcgaggatca gcgggaatgt  
2641 gtgtccagac aggagtacag gaagtacgga ggggccaac tcaaccgtct aaaccaggg  
2701 aactatacag cccggattca ggctacctcc ctctctggga atgggtcatg gacagatcct  
2761 gtgttcttct atgtccccg caaaacgacg tatgagaact tcatgcatct gatcattgct  
2821 ctgccgggtg ccattcctgct gatcggtggg gggctgggta tcatgctgta tgtcttccat

FIGURE 1A

2881 agaaagagaa ataacagcag gttgggcaat ggagtgcgtg atgcttctgt gaaccccgag  
2941 tatttcagcg cagctgatgt gtacgtgcct gatgaatggg aggtagctcg agagaagatc  
3001 accatgaacc gggagctcgg acaagggtcc tttgggatgg tctatgaagg agtggccaag  
3061 ggtgtggtca aggatgaacc cgaaaccaga gtggccatca agacggtaaa cgaggctgca  
3121 agtatgcgtg aaagaatcga gtttctcaac gaggcctcgg tgatgaagga gttcaattgt  
3181 caccatgtgg tccggttgct ggggtgtgta tcccaaggcc agcccaccct ggtcatcatg  
3241 gaactaatga cacgcggtga tctcaaaagt tatctccggt ctctgaggcc agaagtggag  
3301 cagaataatc tagtcctcat tcctccgagc ttaagcaaga tgatccagat ggctggagag  
3361 attgcagatg gcatggccta cctcaatgcc aacaagttcg tccacagaga ccttgctgct  
3421 aggaactgca tggtagccga agatttcaca gtcaaaattg gagatttcgg tatgacacga  
3481 gacatctacg agacggacta ctaccggaag ggcgggaagg gtttgctgcc tgtgcgctgg  
3541 atgtctcccg agtccctcaa ggatggtgtc ttcactactc attctgatgt ctggctcttc  
3601 ggggtcgtcc tctgggagat cgccacgctg gctgagcagc cctaccaggg cttgtccaac  
3661 gagcaagttc ttcgtttcgt catggagggt ggccttctgg acaagccgga caactgccct  
3721 gatatgctgt ttgaacttat gcgcatgtgc tggcagtata accccaagat gcggccctcc  
3781 ttcctggaga tcatcggcag catcaaggat gagatggagc ccagcttcca ggaggtctcc  
3841 ttctactaca gcgaggagaa caagcctccc gagccagagg agctggagat ggagctggag  
3901 atggagcctg agaacatgga gagcgtccca ctggaccctt cggcctcctc agcctccctg  
3961 cctctgcctg aaagacactc aggacacaag gctgagaatg gcccgggccc tggcgtgctc  
4021 gttctccgcg ccagttttga tgagagacag ccttacgctc acatgaacgg gggacgcgcc  
4081 aacgagaggg ccttgccctc gccccagtc tgcacctgct gatcctcgga cacaccgaag  
4141 cacgcgccaa cagtaacgtg tgtgccccac tcgggtgggcg ggggggcggg gaggggagag  
4201 caggttgtaa caatctatc acaagcctcc tgtacctcag tggatcttca gacctgccat  
4261 tgctgcccac gggagacggc ttctctgcag taaacacatt tgggacctc cttttttcaa  
4321 tatgcaagca gctttttatt tcctttaccc gaacccttaa ctgacatggg cctctgcaaa  
4381 ccttaatgac aacacttaat agcaacagga cactcgagaa ttgagtctct tcgttctctg  
4441 cctttttctc tcctctgcct tcctctctct ccctctcccc ttccacttcc acgctctcct

FIGURE 1B

```

1 mksqsgggsp tslwglvfls aalslwptsg eicgpgidir ndyqqlkrle nctviegflh
61 illiskaedy rsyrfpkltv iteylllfrv agleslgdlf pnltvirgwk lfynyalvif
121 emtnlkdigl ynlnrnitrga irieknadlc ylstidwsl ldavsnnyiv gnkppkecgd
181 lcpgtleekp mcekttinne ynyrcwttmr cqkmcpvscg kractennec chpeclgsch
241 tpddnttcva crhyyykgvc vpacppgtyr fegwrcvdrd fcanipnaes sdsdgfvihd
301 decmqecpsg firnstqsmc cipceggpcpk vcgdeekktk tidsvtsaqm lggctilkgn
361 llinirrgnn iaselenfmg lievvtgyvk irhshalvsl sflknrlrlil geeqlegnys
421 fyvldnqnlq qlwdwnhrnl tvrsgkmyfa fnpklcsei yrmeevtgtk grqskgdint
481 rnngerasce sdvlrftstt twknriiitw hryrppdyrd lisftvyyke apfknteyd
541 gqdacgsnsw nmvdvdlppn kegepgillh glkpwtqyav yvkavtltmv endhirkaks
601 eilyirtnas vpsipldvls asnsqsliv kwnpptlpng nlsyyivrwq rqpqdgylr
661 hnycskdkip irkyadgtid veevtenpkt evcggdkgpc cacpkteaek qaekeaeayr
721 kvfenflhns ifvprperrr rdvmqvannt mssrsrnttv adtynitdpe efeteypffe
781 srvdnkertv isnlrpftly ridihscnhe aeklgcsasn fvfartmpae gaddipgpvt
841 weprpensif lkwpepenpn glilmyeiky gsqvedqrec vsrqeyrkyg galknrlnpg
901 nytariqats lsgngswtdp vffypvaktt yenfmhliia lpvaillivg glvimlyvfh
961 rkransrlgn gvlyasvnpe yfsaadvyvp dewevareki tmnrelgqgs fgmvyegvak
1021 gvvkdepetr vaiktveaaa smreriefln easvmkefnc hhvvrllgvv sggqptlvim
1081 elmtrgdlks ylrslrpeve qnnlvlipps lskmiqmage iadgmaylna nkfvhrdlaa
1141 rncmvaedft vkigdfgmtr diyetdyyrk ggkgllpvrw mspeslkdgf ftthsdvwsf
1201 gvvlweiatl aeqpyqglsn eqvlrfvmeg glldkpdncp dmlfelmrnc wqynpkmrps
1261 fleiigsikd emepsfqevs fyysenkkp epeelemele mepenmesvp ldpsassasl
1321 plperhshgk aengpgpgvl vlrasfderq pyahmnggra neralplpqs stc

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FIGURE 2

```

1 gctcattcat ttccactccg catttctgcc cctcgccggc ctcgcccgcg cccgggactt
61 cggaccagtc tgcgcaactg cgtcgcgctc tcccgcgcgc taggctccgg tggctcgttc
121 ctccggggat cgggtggcgt ttgtcctcgc ctgcggcgat ttgggctttg ctctcttttc
181 tgtacagttt tctctcttct tctgcatctc tgcgtttgca aatggaggcc gacgacgccg
241 acagcccgcg ccggcgcgcc cgggcttccc gactccgcgc ccccgtaggc cgtgctgcc
301 ggcgctgagg ggcgcgcccg cgccaccctc cttgtccacg ccgctttccg aggatcgtcg
361 cctgcgctct tgttttttga cgagagttag gactgagttg gagacttttt ttttcttttt
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481 aggaatgaag tctggctccg gaggagggtc cccgacctcg ctgtgggggc tcgtgtttct
541 ctccgcgcgc ctctctctct ggccgacgag tggagaaaac tgtgggcccg gcattgacat
601 ccgcaacgac tatcagcagc tgaagcgcct ggaaaactgc acggtgatcg agggcttctt
661 ccacatcctg ctcatctcca aggccacaaa ctaccgaagc taccgcttcc ccaagctcac
721 cgtcatcact gagtacttgc tgccttccg agtcgctggc ctcgagagcc tgggagacct
781 cttccccaac ctacagtcga tccgtggctg gaaactcttc tacaactacg cactggtcac
841 cttcgagatg accaatctca aggatattgg gctttataat ctgaggaaca ttactcgggg
901 ggccatcagg attgagaaga acgcccacct ctgttacctc tccaccatag actggctctt
961 catcttggat gcggtgtcca ataactacat tgtggggaac aagccccga agaatgtgg
1021 ggacctgtgt ccaggagacat tggaggagaa gcccatgtgt gagaagacca ccatcaacaa
1081 tgagtacaac taccgtgctt ggaccacaaa tcgctgccag aaaatgtgcc caagtgtgtg
1141 cgggaagcga gcctgcacgc agaacaacga gtgctgccac ccggagtgcc tgggcagctg
1201 ccacacaccg gacgacaaca caacctgcgt ggccctgcaga cactactact acaaaggcgt
1261 gtgtgtgcct gcctgcccgc ctggcaccta caggttcgag ggctggcgct gtgtggatcg
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1381 cgacgatgag tgcatgcagg agtgtccctc aggttccatc cgcaacagca cccagagcat
1441 gtactgtatc ccctgcgaag gcccctgccc caaagtctgc ggcgatgaag agaagaaaac
1501 gaaaaccatc gattcgggtg cttctgtcca aatgctccaa ggatgcacca tcctgaaggg
1561 caatctgctt attaacatcc ggagaggcaa taacattgcc tcggagttag agaacttcat
1621 ggggtctatc gaggtggtga ccggctacgt gaagatccgc cattctcatg ccttggctct
1681 cttgtccttc ctgaagaacc ttcgtctcat cttaggagag gacgagctgg aagggaacta
1741 ctcttcttat gtcctagaca accagaactt gcagcagctg tgggactgga accaccggaa
1801 cctgaccgtc aggtccggaa agatgtactt tgctttcaat cccaagctgt gtgtctccga
1861 aatttaccgc atggaggaag tgaccggaac caagggacgc cagagcaaag gggacataaa
1921 caccaggaac aacggagagc gagcttccct tgaaaagtga gttctccgtt tcacctccac
1981 cagcactggg aagaaccgaa tcatcataac gtggcaccgg taccggccgc cggactaccg
2041 ggatctcatc agcttcacag tttactacaa ggaggcacca tttaaaaacg ttacggaata
2101 tgacgggcag gatgcctgtg gctccaacag ctggaacatg gtggatgtag acctgcctcc
2161 gaacaaggag ggcgagcctg gcattttact gcatgggctg aagccctgga cccagtatgc
2221 tgtctatgtc aaggctgtga cctcaccat ggtggaaaac gaccatatcc gtggggccaa
2281 aagtgaatc ttgtacattc gcaccaatgc ttcagtccct tccattcccc tagatgtcct
2341 ctcagcatca aactcttctt ctgagctgat tgtgaagtgg aatcctccaa ctctgccccaa
2401 tggtaacttg agttactaca ttgtgaggtg gcagcggcag cccaggatg gttacctgta
2461 ccggcacaaac tactgtctca aagacaaaat acccatcaga aagtacgccg atgggtaccat
2521 cgacgtggag gaggtgacgg aaaatcccaa gacagaagtg tgtggtggtg ataaagggcc

```

Figure 3A

```

2581 atgctgcgct tgcctaaaa ctgaagctga gaagcaggct gagaaggagg aggctgagta
2641 ccgtaaaagtc tttgagaatt tccttcacaa ttccatcttt gtgcccaggc ccgaaaggag
2701 gcggagagac gtcattgcaag tggccaacac gaccatgtcc agccgaagca ggaacaccac
2761 ggtagctgac acctacaata tcacagaccc ggaggagtcc gagacagagt accctttctt
2821 tgagagcaga gtggataaca aggagaggac tgtcatctcc aacctccggc ctttctctct
2881 gtaccgcata gatattccaca gctgcaacca cgaggctgag aagctgggct gcagcgcttc
2941 caacttcgtc tttgcgagaa ccatgccagc agaaggagca gatgatatcc ctggtccggg
3001 gacctgggag ccaagaccgc aaaactccat ctttttaaag tggccagaac ccgagaaccc
3061 caacggattg atcctaattg atgaaattaa atacgggtcg caagtcgagg atcagcggga
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3181 aggaaactat acagcccga ttcaggctac ctccctctct gggaatgggt catggacaga
3241 tcctgtgttc ttctatgtcc ccgcaaaaac gacgtatgag aacttcatgc atctgatcat
3301 tgctctgccc gttgccatcc tgctgatcgt tggggggctg gttatcatgc tgtatgtctt
3361 ccatagaaaag agaaataaca gcaggttggg caatggagtg ctgtatgctt ctgtgaaccc
3421 cgagtatttc agcgcagctg atgtgtacgt gcctgatgaa tgggaggtag ctcgagagaa
3481 gatcaccatg aaccgggagc tcggacaagg gtcccttggg atggtctatg aaggagtggc
3541 caagggtgtg gtcaaggatg aaccgaaac cagagtggcc atcaagacgg taaacgaggc
3601 tgcaagtatg cgtgaaagaa tcgagtttct caacgaggcc tcggtgatga aggagtcaa
3661 ttgtcaccat gtggtccggg tgctgggtgt ggtatcccaa ggccagccca ccctggtcat
3721 catggaacta atgacacgcg gtgatctcaa aagttatctc cggctctctg ggccagaagt
3781 ggagcagaat aatctagtcc tcattcctcc gagcttaagc aagatgatcc agatggctgg
3841 agagattgca gatggcatgg cctacctcaa tgccaacaag ttcgtccaca gagaccttgc
3901 tgctaggaac tgcatggtag ccgaagattt cacagtcaaa attggagatt tcggtatgac
3961 acgagacatc tacgagacgg actactaccg gaaaggcggg aaggggttgc tgctgtgcg
4021 ctggatgtct cccgagtccc tcaaggatgg tgtcttcaact actcattctg atgtctgggc
4081 cttcggggtc gtccctctggg agatcgccac gctggctgag cagccctacc agggcttgtc
4141 caacgagcaa gttcttctgt tcgtcatgga ggggtggcct ctggacaagc cggacaactg
4201 ccctgatatg ctgtttgaac ttatgcgcat gtgctggcag tataacccca agatgcggcc
4261 ctcccttctg gagatcatcg gcagcatcaa ggtgagatg gagcccagct tccaggaggt
4321 ctcccttctac tacagcgagg agaacaagcc tcccagacca gaggagctgg agatggagcc
4381 tgagaacatg gagagcgtcc cactggaccc ttcggcctcc tcagcctccc tgctctgccc
4441 tgaaagacac tcaggacaca aggctgagaa tggccgggac cctggcgctg tcgttctccg
4501 cgccagtttt gatgagagac agccttacgc tcacatgaac gggggacgag ccaacgagag
4561 ggccttgcct ctgccccagt cctcgacctg ctgatactcg gacacaccga agcacgcgcc
4621 aacagtaacg tgtgtgcgcc cactcgggtg gcgggggggc ggggagggga gagcaggttg
4681 taacaatcta ttcacaagcc tcctgtacct cagtggatct tcagacctgc cattgctgcc
4741 cacgggagac ggcttctctg cagtaaacac atttgggacc ttcccttttt caatatgcaa
4801 gcagcttttt atttccctta cccgaacctt taactgacat gggcctctgc aaaccttaat
4861 gacaacactt aatagcaaca ggacactcga gaattgagtc tcttcgttct ctgccttttt
4921 ctctcctctg ccttcctctc ctgcccctct cccttccact tccacgctct cct

```

Figure 3B



```

ID 1: 3727   ct0g ttt gaa ctt atg cgc atg tgc tgg cag tat aac ccc aag atg cgg ccc tcc ttc ctg 3786
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4211   ct0g ttt gaa ctt atg cgc atg tgc tgg cag tat aac ccc aag atg cgg ccc tcc ttc ctg 4270
aa : 1243    l   f   e   l   m   r   m   c   w   q   y   n   p   k   m   r   p   s   f   l   1262

ID 1: 3787   gag atc atc ggc agc atc aag gat gag atg gag ccc agc ttc cag gag gtc tcc ttc tac 3846
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4271   gag atc atc ggc agc atc aag gat gag atg gag ccc agc ttc cag gag gtc tcc ttc tac 4330
aa : 1263    e   i   i   g   s   i   k   d   e   m   e   p   s   f   q   e   v   s   f   y   1282

ID 1: 3847   tac agc gag gag aac aag cct ccc gag cca gag gag ctg gag atg gag ctg gag atg gag 3906
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4331   tac agc gag gag aac aag cct ccc gag cca gag gag ctg gag atg gag c-- --- --- 4379
aa : 1283    y   s   e   e   n   k   p   p   e   p   e   e   l   e   m   e   l   e   m   e   1302

ID 1: 3907   gct gag aac atg gag agc gtc cca ctg gac cct tcg gcc tcc tca gcc tcc ctg cct ctg 3966
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4380   -ct gag aac atg gag agc gtc cca ctg gac cct tcg gcc tcc tca gcc tcc ctg cct ctg 4438
aa : 1303    p   e   n   m   e   s   v   p   l   d   p   s   a   s   s   a   s   l   p   l   1322

ID 1: 3967   cct gaa aga cac tca gga cac aag gct gag aat ggc ccg ggc cct ggc gtg ctc gtt ctc 4026
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4399   cct gaa aga cac tca gga cac aag gct gag aat ggc ccg ggc cct ggc gtg ctc gtt ctc 4498
aa : 1323    p   e   r   h   s   g   h   k   a   e   n   g   p   g   p   g   v   l   v   l   1342

ID 1: 4027   cgc gcc agt ttt gat gag aga cag cct tac gct cac atg aac ggg gga cgc gcc aac gag 4086
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4499   cgc gcc agt ttt gat gag aga cag cct tac gct cac atg aac ggg gga cgc gcc aac gag 4558
aa : 1343    r   a   s   f   d   e   r   q   p   y   a   h   m   n   g   g   r   a   n   e   1362

ID 1: 4087   agg gcc ttg cct ctg ccc cag tcc tcg acc tgc tga 4122
             ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
ID 3: 4559   agg gcc ttg cct ctg ccc cag tcc tcg acc tgc tga 4594
aa : 1363    r   a   l   p   l   p   q   s   s   t   c   *   1373

```

FIGURE 4

ID 5: 1      agagtggccatcaagacggtaaacgaggctgcaagtatgcgtgaaagaatcgagtttctc 60  
|||||

ID 6: 56632 agagtggccatcaagacggtaaacgaggctgcaagtatgcgtgaaagaatcgagtttctc 56573

ID 5: 61      aacgaggcctcggatgaaggagttcaattgtcaccatgtg0gtaagaagccaagatgag 120  
|||||

ID 6: 56572 aacgaggcctcggatgaaggagttcaattgtcaccatgtg0gtaagaagccaagatgag 56513

ID 5: 121      acatggacagaaagtatggacagaaaggaccaccctgtatgtccttggccagctacggaa 180  
|||||

ID 6: 56512 acatggacagaaagtatggacagaaaggaccaccctgtatgtccttggccagctac-gaa 56454

ID 5: 181      ttgttgccttgccctcttcccagtgggtagtttccccggtgcattcttgccaccacaga 240  
|||||

ID 6: 56453 ttgttgccttgccctcttcccagtgggtagtttccccggtgcattcttgccaccacaga 56394

ID 5: 241      cccttgagggtgggagcctcgccctcgccctcccaccagaactctgctcctggctacaggc 300  
|||||

ID 6: 56393 cccttgagggtgggagcctcgccctcgccctcccaccagaactctgctcctggctacaggc 56334

ID 5: 301      cccagcaccaccagttccgagaggcgtaggtcatcatgtgggatgccccctccccctc 360  
|||||

ID 6: 56333 cccagcaccaccagttccgagaggcgtaggtcatcatgtgggatgccccctccccctc 56274

ID 5: 361      tgagtccttttcttgattcctccag0gtccgggttgctgggttggtatcccaaggccagcc 420  
|||||

ID 6: 56273 tgagtccttttcttgattcctccag0gtccgggttgctgggttggtatcccaaggccagcc 56214

ID 5: 421      caccctggatcatcatggaactaatgacacgcgggtgatctcaaaagtatatctccgggtctct 480  
|||||

ID 6: 56213 caccctggatcatcatggaactaatgacacgcgggtgatctcaaaagtatatctccgggtctct 56154

ID 5: 481      gaggcc 486  
|||||

ID 6: 56153 gaggcc 56148

FIGURE 5

```

1 gaattccaga tgggaagctga cttcctgctc agccctatta aaaaaaaaca caggctttcc
61 tgcctctgag ccccttcgcc acaaataact tgagtgccat gcacggagggt gccactttgt
121 ggcttagggt ctctcagacc ttgtttgtcc ttcagcccct tggggaggag cccaggctac
181 cacctgctgt ccctaagcct aggaccaggt ggagaccatc gaattgcaga tttagacaga
241 attaaccatc acagggcctc ataccatcct ttttaaagga ccaggccttg atggagactg
301 cagtcgcca cccccaatgg gcttttgcta ctatggaaac actgaaataa ccaacaacaa
361 cactgggtgt ggatgccact gaacacacac acacacacac acacacacac acacacacac
421 tggttgatgc ctctgaaccc caaaagggtc gacctggaagg aatggtgggt gctctgtcct
481 ccattctcagc cgcacatctg aagtcacccc agccacaggc acctgtcatt gtcacagctg
541 gtccctatgg gcttactctt tcctcacgat gctcttattt ttagtcagac accaaagcgc
601 tttattttatt tttagttaga cacatttggc acatttcaag ttttccaact tgtattcgat
661 aaagggaaac aaaggattcc tgtcacctgt cctaattgaa agcttctttg ataaatactt
721 tcggacagtg attcatacta tcagccttcc aaaaggagga aggaaaaaaa aaaaaaacaa
781 aagaaaagag cattcttttg agacactctt attcccttgc acttctgatt tgtttttttt
841 tttttttttt ttatttcggg tccagagatg gaatgggtca aattacattt gacgtcctca
901 ggaaaccata ctcttggtaa aagcagtgcc tgtctcaaat gaaatatggg catggaaatg
961 tgctgcccc tcttggaact acgtctttcc ctacatttct ctcacagcc agcagttgct
1021 gggagtcagg cgccattggg aaatgcccac tggatcccag agtgtggcct gcctttatta
1081 gtaatgtttt gaggttgccc gaggacagac tcttcatttt attggagccc ctagtgtgtg
1141 aaatcttgct ttgacaactg gtatgtagac agatggtgaa atgcaaggat tctaacaac
1201 agcctttaga ttaagggtgt ggctgggacc aacagtaaaa tgagagacca ggcgaacctg
1261 cagtcctccc caggggttga tgattctacc acattttctg gctgactacc caactctatt
1321 ccaaggcagt cttgatgggg aatgaggctt agcccagcaa aacaagacct tctaaccttg
1381 ctcccgaggt tgtctttcct aattttaaac aaacaaggat gtagtttctt caaagctgaa
1441 tgtggttcta aagtgtgtga aatgtgtgtt gatgggtttt taatgatcct agaggaagct
1501 ggcttctcgg tctttctact taatctcaac attttctaa cgttcttta gagctgcagg
1561 tccccacagc agctgcaaga ctgtgtatcc tatcagtcaa agccagatgg tagtctgag
1621 atggtggggc attctgttga aaagctttct gtccctgaa gtttttctcc ctaggaacca
1681 atcctgatga tggggccacga ccaatacact cagcagttgc caggcacagc tggatcccct
1741 ctccagtgct gctacctact cttagggccc tggggtccag cgacttgatg tagcatcctg
1801 atcttttaca gactggaaag tgtggcaact gagaagtatg cgctgagagt caggtgaggg
1861 actcaaacc tcaatcatac tccagataaa actgatcagg acgatgtcga accctacctg
1921 cagcccaagc tgagatgagg ctcccctcct ctacgtctga catgctagcc tccccagga
1981 ggaggccaca catttttcat tttagaaata tagatcaaga agaaattgta aagaaagaga
2041 actccttgca aatctcacta ggggtgcctg atgctgacat cttcaatgtc caatccaatg
2101 tactaacatc agtacaatta agaaagagag aagcagagag agggggagaa ggaagggag
2161 gagaacggga tggaggggtt gaggaatgag tatgtgtgca cgtgcacaca gaccgtctta
2221 tacaatttag accagtcaa ggcttctctg aattgcctcc acctcaaac gccttcccct
2281 gctactccca ccttagcttc ttccgcactt tcttcccca ttttaacacg tgggtgtcctt
2341 ttcagactca tttggctgta ataaaatata cagaaaacaa acaaacgaca aaggataaag
2401 gaggtttatt ccgtttacaa ttccagggtta cagtcacatg tgggtgggaaa gtcagcagca

```

FIGURE 6A

2461	ggaacttcag	agaattgggc	gcacacatc	cacagtcaag	agcagagaga	aatgcataca
2521	tatttgctgt	cttgtttgct	ttctcatgtt	cagcttggat	ttctccattc	ttttatagtt
2581	caggactcaa	tgcctaggga	atgacactgc	ccatagtga	ctgggttccc	ccacatcaat
2641	taacaagaat	tgttgaggaa	ttgggtggc	ttgtggacat	ggtttttttt	tggaggatta
2701	tcttagttaa	gctaattgat	ataagcagaa	ccattcccta	ggcaatgatt	ggcctgtggg
2761	catgtcaaca	tttcctagga	atgttggcct	gtgagtatgt	ctgtgccac	aagtaagaca
2821	attggcta	tgatatgaga	aggcccagcc	cactgtaggt	ggtaccattc	cttaggctgg
2881	agatccttga	gctgtaggag	agaggagaaa	tcaaactgag	cacaagcaag	tgagcatgtg
2941	tgcactcttc	tgctctttga	ctgtggatgc	tatgtgactg	ttgtttgaag	tcctgcctca
3001	actttccac	agtgatgggc	tataacataa	ttatatgctg	aatgaattc	ctctctcctc
3061	taagttgctt	tcgttggtgt	ttttattaca	gcaacagtta	aagtagaaca	cttattttaaa
3121	acctatggaa	ggatatatag	atagttttaca	gcttttagagt	tgtttagagt	gagaacacta
3181	ctgtaaacag	tagtttccag	ttctgagatc	agtggccagg	tgtatacatg	tactactgct
3241	cactttcagc	tctaaaaaaa	aaaaaaattg	gggctcagcg	gttaagagca	ctgactgctc
3301	ttccaaaggt	cctgagttca	aatcccagca	accacacggg	ggctcacaac	caccataac
3361	ataacaaggt	ctgatgcctt	cttctggagc	ttctgaagac	agctacagt	tactcacata
3421	taataataat	aaataaatct	tttttttttaa	tctatcacca	tattgcaaag	tagtgtcttc
3481	cattcctatc	aatatgtgag	acccagtttc	tcattctttc	tttgtttgtt	tgtttaagat
3541	tttattttatt	cattgtatgt	atatgagtac	actgtagttg	tacagatggg	tgtgggcat
3601	catgtcattg	ctgggaatta	aattcagtag	ctccgctggc	tccggccccg	ctggctccag
3661	cccaaagatt	tatttattgt	tagacctttt	aaatatatca	cataatagtc	tttatacaat
3721	agataagtg	tttctcagta	ataacctctt	aacagagttt	ttatttttta	tttttaacag
3781	agtttttttaa	agagccaaca	ttcttaactc	tgtggctgta	tttttgcttg	tcctgtttta
3841	aaacaagctc	ttgggtgggtg	gtagtgcaca	ccttttagtcc	cagcagatac	tggcagatcc
3901	ctatgaactg	gtcgagagag	caagttacag	aaaagtcaag	gttacacaga	gaaaccctgc
3961	taactaaggt	tgagatctgc	tatgtctaga	tggcttatct	gagctcagt	caaatgggag
4021	gactctatac	catctgggct	tccccttctc	tgacctgtgc	taggggactc	cctatactct
4081	ctacctggga	aaggtcaagt	agcctcgga	gaccaacaaa	cttctctttt	tccgcagaag
4141	aaccaccca	acaagtacct	gggattcctg	aatgcctct	ccatacaaat	gaggaattcc
4201	aagaacttta	aactctaacc	aatgattttc	atttaccctg	aaaactcctt	cacactctcc
4261	aaggtcctgg	tttaccctaa	ataaagtgtg	ttcgtacaag	ccccacccta	gtagagggtat
4321	ggaggtatgc	tcacaaacca	agatcggcta	agagagctgt	tttcattgaa	gattgttggg
4381	gaaggccttc	ttctaaaaga	gctgtaactc	taagatcctt	cgggaaggcc	ttctctccct
4441	tccctcccc	tccccccact	agcactcact	cccagcagga	ccctaactct	gtataaccct
4501	ccccccccc	ccattctgga	cactgtttca	tccttcccac	ccagtgtgca	gtggcatctg
4561	gatacctccc	tgactatgtt	tcatacagtc	aattctgagg	aagccccag	attagcaagg
4621	ctgaggttct	ctggggccta	tagaacttgt	tgccaggtga	tagaacttgt	tactgggtag
4681	tgtgggctgg	tttgagcaaa	cctgggtatc	tttggtttca	ggttttgggc	ccttccggca
4741	gcacctagtg	aattccagct	gggaagccgt	gaaggtaa	cctgccgttt	gcccccccc
4801	ccccccccc	ccgggccaac	ctgggttcct	ctgtggctct	tgggaaaccc	caatgccaat
4861	gcgcgggact	cctaagaaac	cagagtcacc	ttggaaggaa	ggcaagcagt	gggccctgg

FIGURE 6B

```

4921 aagaaaggct tgtatttgggt cctggaatgg tgtgacttgc ctggtcagggt acttctctcg
4981 tttgtccagg gacactccta ggtgggacca aggcccatgt aggctctact ctacgtaggg
5041 ctagattctt gccctctctt cctttggatg tggggctctgg ggaaagtcat tttcaccagc
5101 tcttgtcctc acctacgcat gcggaagtga taacatggat gtctctggcc tccactgaca
5161 gctcaggggtg agggcagcct tgtccacact gctctgtgtg agcccagcat ggggcgtggg
5221 tgagaacctg gccagtgtct gtgactgtcg acagcacgct tgcttttgag gacatagcta
5281 accaggagaa ggggaagtcct ctgaccgcc actgtgcata ggagggcagg actccctggc
5341 ccacccccac ctccctaggt caactgtctg ccatcagtcc tcatgtgggt gtcacttaga
5401 ggctctgcca attgaaagct gcctgttcgc acttggtctt caacttcaca ctgatgttgg
5461 accaagccaa atgtggggcc tggagtctat tctcagagtt tcccaggcca gctgagaaac
5521 gcagcaaagc tgctagcgct atgcactcac agccaccgtg gcactgactt tgtggctctga
5581 caacgcagag gcaggcagga gactcttgat ccttgagtta gcatttgggc ttttgccttt
5641 ccaatcataa aaaagcccag agacccttgg actcattgcc aagccttgct ctggtaacaca
5701 aggaagacaa gaggccagga ccagactttc atgagctcct ggctttctgc aaccagtatt
5761 tgatcagcag gacttctgcc aagtcctcag tagtcccaga cccttttgtt tctttctgca
5821 gccgtaaaaca atggaaaaga gccagactgc ttctgggttc tgggttgccct ctcagtttcc
5881 ccagttgcaa gtatggcat tcaaaaacct tgctcgagtt ttgatgcctc cgtttcccaa
5941 tttaaataaa tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgagagag agagagagag
6001 agttgaggaa gtcacatgac atcccaaaga cctcttgggc atgctgatag agctcacagg
6061 ttgtccattc ccaccaggag gcttttctgt ttgtctggta cacagctgca gacatagggg
6121 atgagggta gatcagcaca ggaagtggca gaagggagag gggtaccta ggtggttggg
6181 aaacccaggt gcttgggact gctagtaatc aaagtcacct tggaggggaag gcaagccagt
6241 gaccactgga agaaaagttt gtctttggtc cttgggtggg gtgacttgac tggtcaggta
6301 cgtcttccat gtgtgcagta aagaaaagtg gctaaggagg ctcaaggctc attagcttg
6361 gtgaagcaaa ccagacagac acagggactg gggcttgcct gaaggcatat agtcagacat
6421 gcagacagcc aaggatagct ctgaaaagtg cacacacata cacactcaca tgcactatac
6481 acacacacac acatacacta ttctacaca catataccac aaacactata cacataccac
6541 acacatacac tcacacacac tatacacaca ccacacacat atactcacat atactataca
6601 cacacacaca tgcactacac acacatatat acacacatac actctcactc aggagctata
6661 ggctgaggaa agcaagcata cactggaatg gcaggtaagg acaaaatctg tgttaagggc
6721 tggaggtatg gcttagttag tagagaactt ggttgcatgc atgtgggtct gggtaacatc
6781 ccagcactac ataaaatcag gcatggtgtt atacctagta ctagggaagt agaggcagta
6841 gaattggaac ttcaaggcta tgccttgact gctgcagact ctcatggagt ttttgtgaga
6901 attttaaatt caaattctgg gtttggcatg gtgacccatg cctttaatcc cagccagcat
6961 tcaggaggta gaggcaggca gattactgtg ggtttaaggc tagcctggtc tgtacagtga
7021 gttccaagac aggaatatat agagagagac cctgtttcag aacaaacaaa aataaaactc
7081 aaactttctta caaagaaatg tgaactatca gttcctagcc taagatcacc tgatacacia
7141 gaaaataaaa taccatgtta aaaaaaatca gtagatgccg ttttaaaaaa cagaattata
7201 accaggcagt ggtggcacat gcctttaata aaccagcac ttgggaggca gaggcaggca
7261 gatttttgag tttgaggcca gcctggttta caaagtgagt tccaggacag ccagggtctac
7321 acagagaaac cttgtctcaa aaaatcaaaa aaaaaaaaaa aaaaaagata gcagtctgag

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FIGURE 6C

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7381 aaattagaac tatagctgac ttaaaagaca gcttagatct gtggtcagtg aaagatactg
7441 ctcacaagag actgtatcac ttgagtcac ttgcattaat gtccctagta agtaaatata
7501 ttgagagagg aagtaggtta gtgataggct aagggtggaag gacacagtaa atgaatgtga
7561 agtttcctta aagtacattt atttatttgt gtgaccatgt gtgtgtgtgt ctgtctgtct
7621 gtgcacacca tggcttgccc atgaaggcca aaggacaaca ggtaggaagg agctagaact
7681 ctccctcccc tgtataggac ctagggatgg agctcaccac agacatcggt tttgggcatc
7741 aggaaccttt accccgagcc tctcacatac ttcttttagga ttcttttaggt tgaattcaa
7801 aggcctctggc accgattgcg gtgatgggtg gttgtataac tcttgatggt gatggttata
7861 taactgagca tactgaaaga tgtggagtta aatagggtaa gtacgtggaa tgtgaataag
7921 ctatctctta ggagatagat gataggaaga taggatagat agatagatag atagatagat
7981 agatagatag atgtgattag atagatagat agatagatag atagatagat agatagatag
8041 agatagggtga tagactttac ccacatgtac acatatatag ctgttcagaa acagacgaag
8101 agaaattagt aaactagaat ctagatatgg agatattatt caaaggacaa tataaagcatg
8161 ggcaaacaaag catagagggg ataattgtaa tagtaaaagga agtttctgtt taaatagaat
8221 tccagaggaa aataacagcg agaattggaag aaaacctctc tcaaataac agctacaatg
8281 tatgggattg gaatagggtt ggtcccatag actcctgtgt ttgaatgctt ggcccacaag
8341 aagtggaact gttaggaggt gtggccttgt tggatgtttg accttggtgg aggaagtata
8401 aactgttagg ggcagacttt gaagtctcct atgctcacgc tatgccatt gtggcacacg
8461 gtctcctttc tgttgctgtg ggatcaagat gtagaactct tgggctgggt agatggctca
8521 gtgggtaaga gcacccgact gctcttccta aggtctggag ttcaaatacc agcaaccaca
8581 tgggtgcaca acaccaccg taatgagttc tgatgccctc ttctggtgtg tctgaagaca
8641 gctacagtga acttacatat aataaataaa taaataaata aataaataaa taataaatct
8701 ttaaaaaaaa aaagatgtag aactctcagc tccttctcca gtgctatgtc tgcctggatg
8761 ttgccttgct tcctgctctg acaataatgg agtaaaccct tgaaattgta agccagcccc
8821 caattaaatg ttttccttta taaaagttga cttggtcatg gtgtctcttc atagcaatgg
8881 aaaccctaac aaaggcaciaa tgggttaagaa tattccagag ggactggaga gagatggctc
8941 agtgggttaag agcactgttc ttccagaggt cctggagttc aatccccagc aaccacatag
9001 tgggtcacaa acatttgtaa tgggatctga tgccctcttc tgggtgtgtc aaagactgta
9061 ctcacattca taaaataaat aaatctttta aaaaatttcc agaactgatg aaataactga
9121 atccacagag atagaaataa agaaaatcca cacctaaaca tagtagagtt ggagactgca
9181 aaagactgat taaggcttta gagtagccag agaggagatg gcttacttac aaaaatggat
9241 actctaacta gtatgtctagg gctaactttc tcaaaaatag caatacaagc tcaaaagcag
9301 tacagtaata acctacagaa tgccaaaatt gtatgtgctg aacagaaacc gtgtagctag
9361 gagatcattc ctcgagaata aggcctggggc tggagagatg gcttcgtggt taggagccct
9421 tagcggttat gctcttcctg aggacctgag tcaattccca gcgcccacgt caggtagttt
9481 ccaactgcct ttgatccag ctccaaagtg aacctctaac ctttgggagc acttgcgttc
9541 acgcaagtga acacatacct ccctatacac atacacataa ttaaaaataa aaataaatct
9601 tttttttttt ttttaaagaa taaggctgga gtaaaaacat tttcacaaaa ataatgtca
9661 ggtttactct cagaaggatg acacaagggg actgtaaaaa ggacacttgt cagaagagaa
9721 gaaaattatc acaaaaatgg tgtcttagtc aggggtttat tgctgtgaag agacactgtg

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FIGURE 6D

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9781 aacacagaat tgggggtggc ttatagtttc aggggttcag tccattattg tcatgacaag
9841 aaacatggag gtaggcaggc agacaaagga caggagaagg agctgcgagt tctacatctt
9901 gatccacagg cagccatagg agactatatg ctatactgtg catacctcaa gcataagaga
9961 cctcaaagtc actatgggga atgcttgccc catagtgact caatttctcc aacaaagcca
10021 tacctatcca acaaggccac acctcttaat atagtgtcga atagtgtgc tccctatgga
10081 ccaagcattc aaacacagga gtctagagtc ttatgagggc cattcctatt ccaaccactg
10141 cagatggtat agaaatcact gggaagcctg gcagtggtga cgcagtcctt taatcccagc
10201 acttgggagg cagaggcagg tggatctctg agtttgaggc cagcctgggc tacagagtga
10261 gttccaggac agccagggct atacagagaa accctgtctc aaaaaacaaa aaaacaaaaa
10321 caaaaaaaca aaaaaacaaa caaaaagaaa gggagggagg gatgaaggga gagagagaga
10381 gagagagaga gagagagaga gagagagaga gaaagaaatc actgggaaat ggtgagtctg
10441 agggtagaaa tctgtaccag caccaggcag tgatggcaca cacttttaat cccagtactc
10501 aagatctggg ggatgtctga gttaaaggcc agccttatgt acagagtggg acatagatca
10561 accaaggcta catgaaaaaa ccctgtcttg aacatcaaaa caataaaca acataaagtc
10621 catatcagca ttgtttgtaa catgtaatag tagtagttcg taattccagg atggaactaa
10681 aattcacaa acgtcaaagg tgggtggtct tctccctcca gtgcccctca ttgtcggtag
10741 acttcaagct catctccacc atctcttcag tgacagggtc tggagcaggc tctgctcaat
10801 cttcttgctt ttaataggac caaaggatgg tgactagaca cacctgcac gccacctgga
10861 aagtggaggt cccgagatgg ctggctatgc ccaggctctt ggtaccccag ttggccttcc
10921 ttttggcccc tggactctag gtcttgcatc tattctccct tccttgtgtt ttcccttggg
10981 accaagggtg ttgcaaaactc tttgtcttca atgtgcaggg ttgttttgtc cccacgggtc
11041 aacttaggtt atcctgtgtc ctgtctaaca cctcagtggg ctctattttt ggttcagcat
11101 cttcctattt ggttttcagt agtcaactgaa agtgctggca aacagttaac agtgtcttta
11161 gtaggaatgg ttatctaagg gaccatacta ggtaaagggc tgagatactt catatacata
11221 gcataccctg actgctgtaa agatagaaaa acagactgag atgccctaca cagtctgtgt
11281 ctgtataagc tacacacttt ctgtaatggc caacatcaat ttatctttat cccatagagg
11341 gcctggcctg gagcatgtgt tccagggact gaatcatttg aggtaggagt gaatactttt
11401 ctttctatcc tcttgcatc ttccagtaaa attaaagctt atcgctatca tgtatgttcc
11461 caagcaatgt ttaattatct gtaaaaagct ttgtatctga gactgcatgg attacagatg
11521 ggaaaggaaa aaaaagtgtt tatttccaca gtgtctcact tccaagaatg gggtagagta
11581 ttgacaaacc atcacacgaa gacatttttt tttaaagatt tatttattta ttatatgtaa
11641 gtacactgta gttgtcttca gatacaccag aatagggcat cagatctcat tacgggtggg
11701 tgtgagccac catgtggttg ctgggatttg aacttcggac cttcggaaga gcagtcgggt
11761 gctcttacc actgagccat ctcaccagcc ccgacattat ttttttgggt gcagccactc
11821 ataaatggga gaagaatgtt gaaaggaaaa gaaaatgtag gggctggaga gatggctcca
11881 tgggttaatag cactgactgc tcttaccgag gtcctgagtt caattcccag caaccacatg
11941 gtggttcaca accatctgtt acaggatctg atgccctcct ctggtgtgtc tgaacacagc
12001 aagtgtgtgc tcacataaaa taaataaatc ttaaaataga aaaaagaaaa gaaaatgcag
12061 aaaaataata tgaagtctaa aagttcacag cgaaagaggc attttctgca aagttcccaa

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FIGURE 6E

12121	gcaagtgact	ccatgctggt	tgttgatcag	cattgtgagc	cctcgtgttt	aacattgagc
12181	taccccatat	tccacaagcc	caacgctcct	tcagtgcacat	atgcagcagc	tgcatcatca
12241	ttgcccatga	tctagattct	aagctctagg	tgtgggtggt	tgaataagga	tggtcccat
12301	agactcatgc	cagggaatgg	cattaggagc	tgtggcctcg	tgggaggaag	tatgtcactg
12361	aggggtgggt	aataatatag	aagttagtac	caaggactgg	ggtttttgct	gccctaggct
12421	ggaccaagtt	tcttggtgga	atgtggactt	tggattagga	aaatagttga	atgggttcaag
12481	tagagcatca	caggccatcc	tggtaagacc	atggaagatg	gtgctgttgg	tgacatgaat
12541	tatggggtac	acagggttta	gaggagaaga	attgtaggcc	tagatttttc	aaacctact
12601	tttaataagg	gttcttaaac	gctttatcct	ctcttctagc	ccaccacca	ccagagggag
12661	tggaaaggaa	agggttaata	agcaaaggag	ggtgtggatc	tgtttagaaa	aagttctttg
12721	gagcaaatcc	aatctgtggt	accaggatat	cagcagtaca	gttcactcag	aacagcagca
12781	gcagctcgat	ccacttgcaa	acaccattca	tgaatcagca	atggcaggct	aatccagaag
12841	aaacctcgag	gctctgcca	gtacaaggaa	gcagcagcaa	gaagctgcca	gaaagaacac
12901	caccagaagt	tcttttgtgg	catttctgtc	tatgaagtca	tatcaaatga	tgactagcaa
12961	agaatggcaa	ggcaagggtc	tgggtgagatg	gcttagcagg	taagagcact	gactgtctct
13021	cccaaggta	tgagttcaaa	tcccagcaac	cacatggtgg	cttacaacca	tcgtaatgag
13081	atctgatgcc	ctcttctggt	gtgtctcaag	tcaactacag	tgtacttatg	tataataata
13141	ataaataaat	taaaaaaaaa	aagaatggca	aaccaaacca	tacagcttca	tcagcgaaga
13201	ccagtgtcag	caaaacccaa	tgataaccag	caaataatata	tatcctttcc	aaacatcaca
13261	ttcttgttct	ctcaagtgtc	agcttttagca	aaacatcaca	tgccctttgc	ctgactgtct
13321	tctagaaaac	caccgtgtat	ctgttctcag	caaaacatcc	tcccacatgt	ctgcttcagc
13381	aaaaacatcc	tctcataaga	cagtttccag	aaaaacatca	catgacatga	ctgcatctcc
13441	aaagaagcca	gaaatttcca	attcaaagag	tactagtatg	caacctagag	accattcttg
13501	tgatattttg	acaaagatca	tgggtacatt	ctgctcttgt	catgcacaca	gacacacaaa
13561	tctgcctgag	gttaaataga	agagttatga	atgaacatct	ttagaagatt	tgtctctaag
13621	agattttcaa	aaagtttagt	attgactttg	ttgcttggtt	attagtgacc	atacttatgc
13681	agatctgtaa	cgaagaggac	caagctaaac	aaggaacata	cagaatgtac	agtttgagga
13741	gaaaaggagc	ccagggaagt	gtaatggagt	caagtccagt	gcttgaggag	ataaacctga
13801	tgttaaatgg	aaaggagaag	tgggtgacct	aagccaggac	tccacctagc	taagcttcca
13861	acttctgaga	agtaatcaaa	gaaaagttta	gaactgggtg	tagctgaatt	accttgaatg
13921	ttagcagcac	tcatgagaca	gaggcagcag	gcaggctcact	gagttcaagg	ccagcctggt
13981	gtacagatgg	ggttccagga	cagccaagct	taggcagtga	aggaaaccac	tgaaaacaga
14041	aagctgggtg	agatggattt	gaatgaagag	gcacattcca	ggcccagcag	cagcagaact
14101	tggtagcttt	ggccatattg	ctctggcttt	agagtggagg	gtacaaaaaa	aagagttatg
14161	gaatctccct	ccgtgactaa	ggaaaagtga	tggggccagg	tgtgtgtcag	ggatgtttct
14221	gcatggagac	ccagagacct	ttgcttaaa	ttgtgcaggt	aaaaacctgg	attgttgtga
14281	tagtttgaat	gcttggccac	agggagtggc	actattggga	ggtgtggcct	tattgaacga
14341	agcgtggcct	tgtttagagga	agtgtgtcac	tgtggaggca	ggactttgaa	gtcatatatg
14401	ctcaagctct	gttcagtgtg	acatacatto	tccttctgat	gcctccagat	caatatgtaa

FIGURE 6F



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14461 aactctcagc tcctccagca caatgtctcc ttggatgctg ccacccctcc cgccatgatg
14521 ataatggagt gaacctctga aactgtaagt cagccccaat taaatgttat gagttgccat
14581 ggtcatgggtg tctattcaca gtgatggaaa acctaactca gacgattgcc ccagaaagcc
14641 cccaagatgt tggatatgcc agagtcattg gatttgtgaa gagggatgct gttaacaggg
14701 agtggaaactg gcccagaga aataactgtg ttgcagtc aaagttgaa aagagttgga
14761 gatctgaaga ctgctttgac atcaggcacg gagatgcaga gtttgagtt tacacagctg
14821 ttttttggtc ttgcttttgt ccagtttttc ccttttgga tggatgata
14881 tatcctgtat atgttgaag tatgtgatct tgattttgat tttattccag atcatagtta
14941 agagcttgcc ataagtcctta gaacagactt tggactttta agcagggtta agactgatag
15001 actatggaga cttttgaggt aggattgagt gcatttctgg attatgataa agctacaagt
15061 ctgtggggac tgggatgtag aatgtggtgg cttgaaaaag aatggccccc acagacacat
15121 acttgaatgt ttaaggggta tcattagaag gtgtggcctt gttggagtag gtgtggcctt
15181 attagaggaa gtatattatt gggtttgggg ggtgggtgagc tttgggtttt gtctttgtgt
15241 atgcctgtat gaggaggtca gatcttttga gactggagtt acaggcaatt gtaagtggc
15301 atatgggtac tgggaattga acccaggtcc tctggaaaag cagccagttc tcttaaccac
15361 tgagccatct cttcagtcct gttccaatga atttttgaga agcttttcta gaagtgcctg
15421 aaccagaga gacaataaaa acagttgttc tcaacctgtg agttgagaca cctttggggg
15481 ttgcatatca gatatttatt tacattgatt cacaacaatt gtaaaacttt cagttttgaa
15541 gtcgcaatga aataatttta tggttggggg tgtcattaca acatgaagaa ctgtattaaa
15601 gggtcacagc attaggcagg ttgagaatca ctgcaacaaa agaagaattt tgtgccaggt
15661 ggtagtggca tgtgtcttta atcccagcac tcaggaggca gaggcaggca gatctctgag
15721 ttcgaggcca gcctggtctt tagagtgagt tccaggacag ccaaggctat acagagaaac
15781 cttgtctcaa aaacaaaaca aaacaaaaca acaaaaataa ggtattttgta aaacataccc
15841 tagatccgtt gtgctaagac ataacagcat tccaaatata catagcccaa gtagccaagg
15901 ggtagagct cttatcagct ttgatgagct tgatataagg ggaatttccc tttatcccca
15961 aagatgaagt ggtcttaacc ttcttgcagc ctgtttgctt gttagttaat aggtttattt
16021 ttattttatg tatgtgtgtg ttttgcctga atatatgctg tgtaccttaa gtgtacttag
16081 tacatgagga gtccagaaga gggcgccaca tcccacagaa ctggagttac agatggttgt
16141 gagctgctgt gtgggtgcta ggaatcaaac ctgggtcctc cagtgtctct aactgatgag
16201 ccactctctc agccccttcc atgattcttt aaaaagcagt catagtgaag agagtacaag
16261 gttgtgcac aggcagtaa ccccccaat ccatttctgt aacaagtcag agtaagatga
16321 cagatctttc aaagggacac cagcaactgt ctgggcccct cctgtaggtc cccctaaact
16381 tcactttagt ctggagaaat tccagggtcc tcagattact ccagagagct agaaagagaa
16441 gcttttcttg tctcgttttc cgtttgtgtt tataacataa actttttatt atttatttat
16501 ttattttatt atttatttat tatatgtaag tacactgtag ctgtcttcag acactccaga
16561 agagggagtc agatctcgtt acggatggtt gggagccacc atgtggttgc tgggatttga
16621 actcgggacc tttggaagag cagtcaggtg ctcttaccac ctgagccatc tcaccagccc
16681 tataacataa acttttaatt tcaactggaa gacattcaag cagaggtccc aagttctatc
16741 actcagaaca catatacaga tctggacata ttgacatgca catgaaatgc aatggagata
16801 gagagacaga aggatccctg gtacttgctg gccaccacaga ctggtagaac cagcaggctc

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FIGURE 6G

16861	caggtagctt	cccaaccatt	tctccatctt	tgggtccatt	gttgccctgtc	tgaatatctt
16921	tgcagatagt	tttttagagg	gaaatacagc	aagtaagcag	aatgggtgcag	ggtagagcct
16981	gcacctggaa	agtggagaaa	catcctagag	agacacagcc	ttgcaaggct	ggtccagggt
17041	gtgggcagtg	tacagctgtg	actgcagatg	tcagcacaga	tgctgggtac	ctgattcatg
17101	gcaaccacag	gttgggaggg	cccctacaga	tggtggagcc	ccagggtctga	caatcccagt
17161	ggggtgattt	gtgacgtttg	taataagatc	agatgtgagg	gtagagggtga	gagagagggc
17221	ccaggtagcc	ttctagacct	gtctttggaa	tctgagttca	gactgggacat	tttgggggct
17281	cattttccaga	gtcactctcc	tgtgctctgc	tcccatattc	atgagaagag	cactcccatg
17341	ctggcagaac	atgaggccca	ggaagaagac	atggggctct	ccataactca	accccagaga
17401	cctagtgcc	agcaattatt	gctcatagca	gccaaaaaca	tgtaagaaac	tgccccattc
17461	tggcgaaaga	gtaagatgca	tttgactgtg	actgtcaccc	attgtcagga	ggccaaagca
17521	tttcttttagc	agctcctcga	gtcaatgaaa	tactgagtgt	actgaggacg	agggcagctg
17581	atgtcctttt	tcactgttgg	tctcagttaa	cagagggtcaa	ccaggatcca	aaaagcagta
17641	ttatgtggaa	actcccagaa	agaaccacga	aaggagtttg	atgggtcacga	gactggcacac
17701	actgccagag	tcgcgtggct	agcgctcagca	aaagttttca	agtgacttcc	acggaagcat
17761	atttacgacg	acgtacagaa	gaagggcagc	tacttaacag	atgcccacct	acctttttaga
17821	acagctaata	agtcacagat	gcctgcggta	ctcccagAAC	agaggggcct	tagtagtcag
17881	gcctcacaca	ggaggcagga	agaaaagcat	gcaggaatca	aaccatagcc	taaagtataa
17941	gatgaacatc	caggagccta	aaccactcta	aagaaaatta	catagatcct	ctatgtaaat
18001	taaggagcag	gagagtgagc	tttaagtgtt	ttctgcaggt	gcataaatta	tgagggcact
18061	tcaggcccta	tggagaactt	aacctcctc	ctcagatgct	ggctgcacgc	ggctgtcctg
18121	ccacaggacc	cctgctatga	agtgagtgca	ggaaagaacg	ttttatagtg	aagatgcctg
18181	agagacttcc	aggccagggt	atccaagtca	acacctacag	tgacaagtct	tggtgatggg
18241	ttgtaccctt	gaaatattat	catgagaagg	gcactctatg	cctctagagt	cttctgcccc
18301	caaccctaaa	gcccagtcctg	atctgagacg	agaaggagac	agattccagg	gaaggcacac
18361	gctctacagt	gtctggccag	tgttccatag	aaccggcAAA	gtcattaaac	acaagaaaga
18421	actgtaggag	atggaacaat	gtgttggtat	gacctagatg	gaccttaaag	gactgctctg
18481	tgtgtgtgtg	taactaagga	acctgggtaa	acgatgcggg	ccttaccact	cttctatcca
18541	ttaaaatggt	tatcatgtct	cttcgtgggtg	gtgcacgcct	tttaatccca	gcactcagga
18601	agcagagaca	agaggatctc	tgagtttgag	gccagcctgg	tctctagagt	tcagggtctac
18661	acagaaagac	cctgccttga	aaccaacca	ccaaccaacc	aaccaatgaa	ccaccataa
18721	cccacagatt	tttgttgggt	gtgcttttgt	tggaaacctcc	ctctcttttc	tcagttttaa
18781	gactccagaa	ccgaagttag	aacagctggg	catgttactg	tgtgcttggg	atcccagcaa
18841	tggggaagag	gagacaagac	tttcctggca	cttattggta	agctagccta	acttacccta
18901	ggtgagctcc	gggcccagtga	gagactctgt	attaaaaaaa	aaaaaagtgg	atgttaaaag
18961	acacctaaag	ttgtcctctg	gcctccacat	gcattgtacag	acatatgcac	acatgtgtgt
19021	gcacacatga	ctgtttcctc	ttgtttatca	cctgtcctta	tgatttgaga	gaactgtagt
19081	aggctttcag	atacagaagt	ggattggctt	ggttaaaaat	cttagttcca	ctactggcct
19141	gtgtaaaaga	tggggaatct	ctgctgagct	aagccatgca	ctatgagaac	agtctctctc
19201	caggccagac	ctctacaaaa	aaaatcccaa	caacaacaac	aacaacacca	ccaccaacaa

FIGURE 6H

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19261 caccttttga ggaaggtgtt ggtaaaggcc ctagtttaaa aatggtgtta catatacaca
19321 ccatgaagt cagagagtcc attcgcaaca ttatttgacc ttcagcacga tttgtttctg
19381 gaactttccc accccattct tgcctcgttc cccaggtcc tgggtactgt tattattttg
19441 tatccatact gttgcacagc aagtgtctag aactttctga atctgcagaa cagactcgct
19501 actgatttaa ccatggcctc cctccccc ccttcccct ccccttggct tctgctgacc
19561 accactctac ttcccatctc tccctcgttg gctgttagct acttagtggg agtgggaacca
19621 tattgacttt tgtgactggc ttacttggct tagtataatg ttttcaaggt tcaaccatgt
19681 cattgagtgc accagtacat tcctaaaacc ctggcactca ggaggctaag gtagggggaa
19741 ccagaccaat ggttttcaac cttcctcgtg ttgcggtgac cccacaacc atatttctgt
19801 tcttacttca tagcagtaat tttgctaatt ctatggatca tagtacaat atttttggag
19861 atagaggttt gccaaagggg gtctcaatcc acagggttaag aacttctgat ttagactttt
19921 agttcaggcc aaattacaca gtgagagcct atctctttca tttcctaatt tgaagaaag
19981 aaagaggagg gggagggagg agggaggggg ggggaaggga gggagggaag ggagggaggg
20041 aaggaggagg gggagggagg gggaggaagg gagagagaga gagagaaaga gagagagaga
20101 gaaagaaaga gagaaagaaa gggagaaaga gagaaaaggc taggcgtgat gcagctcact
20161 gcagctctgt gagacgcagg caggtccatg gtcttcccac ttcagccgcc tagtgaattt
20221 gaggccagcc tgagagataa gagaccctgc ctttaaaaaa caaaatagac aatcagctta
20281 gtgggtaaaa gtgtttgtga ccaaagctgc caacctgtgc tggatcccca gaaccacat
20341 ggtggaagga gaaaaccagt tctgcaagc cctccacgtt gtgagccatg gcatgcaggc
20401 atcctcagac agacagacag acagacaaaa tgaataagta cattaacatg tttaaattaa
20461 aaaatggaag gggcagaaag gggaggaagg cagatggggt cttttgtttc tttgtttgt
20521 gtgtgtgtat ttatgtatat atgtgtgtat atgtatgtat gtatgcatgt atatgtat
20581 gtattagaga caaggtttct ctgtgtagct ctgactgtcc tgaaacttgc tctagggatg
20641 aaatgcatgc accccctccc cccagctgaa actgacagtc tgattcccta ttgtgcttgt
20701 gtttcttacc agttcatcct ctgctggaca cttggatggc atcttctatg ccactgtgaa
20761 cagagctgca agctttcatt ttgggggtat atactcagaa gtgggggtac tgggtcatat
20821 gaccagtcag agattgttta gtaactacca agttctctac atatttagaa atactatttc
20881 ttcttcttct ttcttcttct tttcttctt cttcttctt cttcttctc ctcctctcc
20941 tctctcttct tcttctctc cttcttctt tcttctctc ctttcttct tcttcttct
21001 tcttcttctt ctttcttctt tcttcttct ctttcttctt tcttcttct tttctctct
21061 ctctcttctt cttcttctct ccttcttct tcttcttctt cttcttctt cttcttctt
21121 cctctctctt cttcttctct tctctctct tcttcttctt cttcttctt tcttcttct
21181 tcttctctct cttcttctct tcttctctt tcttcttctt cttcttctt tcttcttct
21241 ttctctctct cctctctct cctctctct tcttcttctt ttaagcttt atgtgtacag
21301 gtgttttgtc tacatgtata tcttgacac cagaaaaagg cactggatc catgggacta
21361 cagttacaga cttgggaggc atgggggtgc tggctcttga actcaggctc tctggaagaa
21421 cagtgtctct aaccactgag ttaactctct ggctccaata tttcatctct ctctctctct
21481 ctctctctct ctctctctct ctctctctcc cctctctct cctctctct tctctctcc
21541 cttctctctt ttctttttta ttttttattt ttctacttat tttcaatage agccacctcc

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FIGURE 6I

21601	acagatacaa	agttctctga	ataggccata	aaaatctgag	cttactcttg	agtaatatgt
21661	ggtgaatgga	cggcagagca	tggcctcttg	tcttgcttgg	tcctcacaca	ggacacaggt
21721	cctcagacag	gcccaggacc	ctagagctcc	tttgggggag	gggacacagt	ggtgctatga
21781	aagcctgtct	tcttctactt	actctcagtt	cattataaag	catttcaacc	tgtaaatggg
21841	ttccagggtc	atactattct	gccttaatta	aactaatccc	cacattatga	tcaagaaatc
21901	ccataaaaaat	gatctgtaac	aacatcacac	ataggagata	aatgaatta	atgtgaatca
21961	cacggaaatg	aggaatgaca	attcctgtga	ccctcccaga	ggcccttatc	aaccatagga
22021	aaaaaaaaaag	agctgacatg	ttgatccaaa	tagaggaaaag	aattaggaaa	agcagttaag
22081	gaaagaaaga	ggcccttaca	gatttacatc	tgcccgataa	agccactcc	aaagcaggag
22141	tcttgcatga	gtgccatgta	ccctaactac	agagcagcag	gggagagatg	ctgaagtgtg
22201	cactgtgccc	tgtgtcatcc	agtcagtggt	caggcatgcc	acgtcaaaca	tttttattaa
22261	cggggcacat	gatcagaaat	atttgagac	agtgactgga	tagagagtcc	ctgtcattca
22321	tcctggatct	tccaggcaag	actgacacat	cagtttgga	gaatcacata	acagatactg
22381	gaagagggcg	ctggcaagca	gcctatgtgg	aggatagaac	ttgacagcac	tcaggcagag
22441	tcacctttaa	ccaacacctc	aggatttctt	cccaagctcc	cctctgtatc	tcttttgacg
22501	ctgcttcctg	aaatgtcttc	cctctaattg	tgtccctgtg	gactttggct	gtccctctgtg
22561	taggatgggt	ttggtatcga	ctgttctcga	ggctgcgggg	aggagatact	tagcagagtg
22621	ccaagagtcc	tccaggggca	gcctcggatg	atgacccggac	tattcattaa	ctcagaaaaa
22681	aatggtgcct	ggaagcatct	taccaagtgt	agttgttctg	cgctcagggt	atgctcgggg
22741	tattgtattg	ttctgtgtgt	atgcttccct	tctcagagga	gttcagttct	catggtcttt
22801	gtaacgtcag	tgttacattg	ttttaatggc	tacatcattg	ccaccaatgg	ctagcctctc
22861	ctctgtctac	cagccctttc	ctttctcttc	ttcagtgtctg	ggctggaacc	caagactttg
22921	ctcatgctag	actaggcaag	ctactcagcc	ccagccttgt	tcatggcact	gagtgtctcc
22981	atatgcccgg	tgagctctcc	caggctctggc	tttcattgct	ctcttcacaa	gcctggatgg
23041	tgttggatac	ctgatggccc	cgggtctctt	tctctccctt	cagggcaagg	ggaacatgtg
23101	atctctctct	ctctctctct	ctctctctct	ctctctctct	ctctccctct	ccctctccct
23161	ctccctctcc	ctctccctct	ccctctctca	ttgttactcc	tgcttggtga	gccaagcaaa
23221	gaaaatgacc	actgaacagt	gaccacgtga	caagttgggg	aaagataagt	agaaaagggg
23281	gcgagaagag	gggaagggaa	ggagaggtaa	gaactatgca	aagaaaggaa	gaaaagggaag
23341	agaaagggga	gggggagaga	aaggaagcag	ggaggaggac	ctctgtacac	ctccaaacta
23401	acccttcaag	atccaaagag	catcttcttc	cctgtggccc	tccagcggcc	cggccttgct
23461	caactctcac	agcaaccctg	agcggagtgc	ttgggtctgc	attgcaccgg	tggggaagcc
23521	gaggcctggg	aggttccaac	ctttgtctag	aagcacctca	tcctccgaga	agatcagcac
23581	tgacagagag	gtcaccacc	tgctctctag	ggccacctcc	ccagagccca	gagaaggatc
23641	ttacctggga	tctgtggcg	gccatctaac	ccagaaggca	tgggggtgcc	tggaaatgcc
23701	aggaaaggaa	gtcaggaaca	gctcaggcag	aatgaaggc	acaaaatggg	ccccacattc
23761	ctggctgaac	tgggatcaag	agtgagcaca	agcttctaag	atctcaggct	ttcttctctc
23821	caacctatct	gctacttggc	ctggaaggag	gatgccaca	gccttccctg	cctcacctag
23881	ccttccatca	cctccttgcc	cctctcctct	cttcccttcc	ttctgttttt	cctttccctt
23941	cacccctccc	ttttctttct	cattcctccc	ttctttcatt	ttctcttacc	cttcttctt

FIGURE 6J

24001	cctttcttgt	ccccctccc	aacaacaaca	acaaatccat	ggcttttgtt	tctaaaatta
24061	tatccgcaca	ataacctctc	tgccaattcc	aggcacacag	agccaatgga	ccagctccct
24121	ttggataatt	caaattgacc	ccaagatagc	cctacccac	ttgtacctcc	tccctttgtt
24181	taagagggtg	ctctaagctc	tttgtttcct	gaccgaaatc	cttccatggc	tccctattat
24241	cccagagaag	tccacacctg	actaagcatt	ccaccacagc	tctgcagcct	tctcaagttt
24301	caatcccat	ccttcctggg	gtggagtgtc	cctgttgtac	ctttggtaga	gattgactagg
24361	gactcatcag	attacaccag	gacagtgtat	gtttggatta	gcagcagggg	tgtgaggcta
24421	gatgcttatt	tgccttgtgg	catgcaggac	acctgtcagc	tgccggagaac	ggctcgccat
24481	accaatttcc	cgaagggcct	cgggctcttg	tgcttccttc	tgctatgatg	ctagcctcgg
24541	ctgctgccac	gtgtgttccc	agcctcctgc	tctggcccat	cttcatctgt	ccacagacct
24601	cagtgttgca	aacatggctt	cttcagatat	gtctccctag	gggtgccccg	cttcaggaag
24661	tacggctgag	agagccatgg	ctctttgggt	cctggtcact	ttgagttcct	ccataccagg
24721	agggtagggg	tggagctcag	agaagaccct	gggcatacag	tcttgggtgc	ctctatctcc
24781	aggcaactaa	ggcacctcac	ccgctatatt	ttgcaggaac	tttctaagct	gggcttaggg
24841	gtggacactg	acatagaact	tcgaactctg	cagctgcctg	tggattacag	ggaggtaaaa
24901	cggaggctta	ccacaatctg	ggaagatttt	caaccacaag	taagtgtatac	ctygagaggc
24961	tgtgggtctg	ggaacctgat	gatgggccc	gggccttagga	actttctgga	ccttgatcta
25021	gatttgaagg	ctggagtaca	cctgaattaa	agcttctgtc	gtgagattct	gggtctgtgt
25081	ataagtttat	gctgaaacac	gaggtagata	gtaaaagatg	actgggggca	agtgggcccg
25141	acaaaatggg	aatctgggat	taaagaccct	aggactctag	gatagctcac	acctatccta
25201	aaaaaagaga	ggccctggat	taagccctgt	gtatggctaa	ttctggctgt	tctgaggaat
25261	ttaaggtaaa	gcgctttggg	cctaggaagg	tctgatgatg	attcaccag	ggttggtcca
25321	ccttcaaaac	atcctgccag	gggcctgggt	tgatggctca	cacttttaac	cctggcacct
25381	gtgagtttaa	ggccagcctg	gtctagttta	tgagttcaca	gccccattcc	aaactaacia
25441	aagtaactac	atagtaactg	aatataagca	ctgtgtaaac	aggggcacaa	tgccagggtg
25501	ggtagctcac	gcctttaatc	ccagcacttg	ggaggcagag	gcagggtgat	ttctgagttc
25561	aaggccagcc	tggtctacag	agtgaattcc	aggatagcca	ggactacaca	gagaaaccct
25621	gtcttaaaaa	acaaaaaaca	aaaaaaccaa	aaaaacaaaa	caaaacaaaa	aaaggacact
25681	gaccaaacac	tgacgcaaaa	tcctctgcaa	ctgttttcaa	aagaggacaa	ataaagtcta
25741	ataagattcg	attagactgt	tgctagcttc	ctttatgaaa	gtttcattaa	atacaggatc
25801	ctgttaaaaag	ccagcatctc	ccagggtcat	cttggatact	tgctttcccc	caactcctgg
25861	ggggaaagag	agcacacaa	ctcggatgag	ccatttgaaa	tacaaaagtc	ctttttaatc
25921	cagaaaaaat	ggggaaaagt	ccttaaatgc	agatgtagca	tgccataatc	aacccaaaga
25981	tgtgttcctt	ttgtatcagc	accattactt	aggggcctaa	gcagggtccc	tgaggactt
26041	ggagctagat	ctgttttagc	gggtctctgt	atcactggac	ctctcttcac	atctagtgt
26101	ctgggtgtctg	tcctgggatt	tctgatatgt	atgtccctac	agcttgttgt	gcatgtgggc
26161	atggactctt	ctgccaaggc	catctttctg	gaacagtgtg	gtaagaaccg	aggctatcgg
26221	gattcagatg	taagaggctt	ccagccggag	gatggagtgt	gcctccccgg	tgcccccga
26281	gtgaggctgt	ctgttgtcaa	catgaaggag	gtctgccggc	gtgtggctgt	tgagaatgtc
26341	gaagtggcct	tttcccagag	tgccggcagg	tacttcagga	ctccgtgtgc	caagtgccaa

FIGURE 6K

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26401 acagatggga gagagggatt atccttcaga gtcccttctc tctcctcaag aggctatcct
26461 atgttggtcca tgtggctgct ttgggtcacag gcatcctatt tggtcacaggc actgcagatt
26521 aattttaacct cttctccaaa cgctgacagc ccctccccct aagcaccttt cctctcttct
26581 agggataaag aaatacccgga ggggagttgg cagtaaggga gtcattgtgg tgaagggtgc
26641 ttaccactag ttgtttgaaa ggccggctca attctgtcat gaccgcttgc tggtcattag
26701 actctgagcc caagaaccaa tgtctgtctg gagtgttctt aggccatgtc ctttctctat
26761 cagaagagcc aaactcaagt ggtactaggc atgtgggcat ccataaactc atgcttcatg
26821 aaacctgtac ttactgtgtc tggcatcgac aagatctggg agtaatgggg agtttcatgt
26881 ggttgcaggt acatctgcga ttacacctac tacctgtctc tgcaccttgg gactgggcat
26941 gcggctctca tccatgtccc tcctctgtcg cactggctct cggccagcct tctgggcaaa
27001 gccttgcgag tcatcatcca agaaatgctg gaagaaatcg gaaaagtcca gactcaaagt
27061 acagcagctt aagggaaagca gcaggggatg gccttcctta gatgaaatgg agtgtttcag
27121 gcttgacagg agaagccagc tgtgttatga gaggctctaa aaaagggaaa cagttacaag
27181 gctgggggtg ggggtggggg tgggggtgtg gactcacaga atcacaatct tactttagtg
27241 tctaaagcaa gaagaaaatc ccaaaggcg gatgcttcat aaaggattaa ctaggggaag
27301 ttatgacctt tgtaactcca aagagccacc aaaacctagt gtcaagacca aatgaactga
27361 ataactctca agtgttcttt gaaaaagatt ttattttatt gtttgtttgt ttgtttgttt
27421 atttattata caatgttctc cctgcatgta tgctgcatg ccagcccagg gcaccagatc
27481 tgattataaa tggttatgaa ccaccatgtg gttgctggga atcgaaacta ggacctctta
27541 agctggcagt catctccct gcttgttttt gttttatttt gagacagggt ttctctgtgt
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27661 ttacaagatt tcctttgcaa ataaaccaag gacattttac atatgacaga gccaagccac
27721 actaaggcag atcaaagccc aaggtggaag ccgggcgtgg tggcacacac ctttaatccc
27781 agcactcagg aggcagaggc aggcagattt ctgagttcca ggacagcctg gtctacaaag
27841 tgagtgccag gacagccagg gctacacaga gaaacctgt ctcgaaaaaa acaaaaaaac
27901 aaacaaaaaa agcccaagggt ggactgggat ggcacaggcc accagcacag aacctagctg
27961 cttggctggg gccttggctg gagaccctc tctgtgagca aagagctcct gctccaaacc
28021 ttaggctcct ttgttccagg agtgggctct agtgacactt caggtcactt ggcacctggt
28081 cagacacatt aaaagaaaac gccgggcata cgccttttaa cccagcactt gggaggcaga
28141 ggcagggtgga tttctgagct caaggccagg gctacacaga gaaactctgt ttcaaaaaac
28201 agaggcccag accccaaccc ccatgagcag ctcttccacc ccctctgcgc ctctccagtt
28261 tctcaagacc ctaagcggcc atttgcatg tattttttgt aaatagcttg gcatcccccg
28321 acaatacaca ctgcatcctg ttcagtcaca gctgatagtg ggtgggtttgt atgcttgcca
28381 gccagtgtag aacactgttt tttgtctggt catttaatgg ttgggaggtc tgaagcatgg
28441 ctctgtgttc atctataaac ccgactaata aaaagtcttg gttctgacta cccagagaat
28501 gtgtcaccaa caacacacca gccaaaaaaa ggaaagaaaa aaaagaaaaa ggtgtagtat
28561 gggccctcag cttgtggctt gaatatcttt ttttgttttg cttttttttt ttgggggggg
28621 ggtgaggtgg gtgggcagca gtatattatg aatctagcta gtaagcagggt gtttaaaaaa
28681 acgaataata aattaattct agaacgctcg taatagggtga cttagctggg caggggtggc

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FIGURE 6L

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28741 acatgccttt aatgacaaag ctccgtagga aggcagggtgg ctctctaagc tctaggacag
28801 cctggtctac agagcaagtt ccaggctcagc cagggctaca cagagaaacg ataattcaga
28861 aagattaaaa aaaaaaagtg tctcagactc caaggagagc acctaactta aaaaaaaaaa
28921 gacttaattt tatgtgtatt agtgtaaagg tatctcacc ttagatctgg atcccttggg
28981 actggagtta caattgtgag ctgccatgta ggtgctggga attgaaccct ggtcttttgg
29041 gagagcacac gtgctcttaa cctctgagca atctctcgat tcctaatagt cttttaaagg
29101 tctagtacct ggctggagag atggctcagt gatttaagag tgccgactgc tcttccgaag
29161 atcccagagtt caccgagttc aaatcccagc agccacatgg tggctcacia ccatccgtaa
29221 gaaatctgat gccctcttct ggggtgtcct aagacagcta cagtgtactt acatataata
29281 aataaatctt aaaaaaaaaa aaaaaaaaaa agtctagtac cttcatcctt aaaagcagct
29341 ggctccggcc aggcagggtt ttggtaaact ggaggcatag taccatcca ggatagcaca
29401 gaaataagac cttcagcgtc atctagttaa gctccctggg catctggtaa acaaaacccc
29461 cggggcagga cgagattgga aggtgtgctc ttccaacgac cttttgacta taaatccaaa
29521 taccatttgg gttaggctac tgggaggtc actgggtctt gagttgcctc tgatttgctt
29581 ctgccacctg tgtctcatcg atcagttctt caccgggtgt cctgattttg tcaactgagtt
29641 ccccatctct cagtgttcag tgaggcggtc acctactctc ccaggagtct agaatgtatg
29701 gcttggttga ttttccaacc caaacattc atcaccttc catggcaaag atggagagcc
29761 agcatctcag agttacctgt gggcaacctc acgactcagc acctgcagc caggaacagc
29821 ccgattttcc ttggttctct ctccagcacc ctcaggcacc ccaactgtga agcactacca
29881 aggacaggaa aatgcacgca gcacgcaagt ttctggcaac cccgccccac cccagactc
29941 acacatacca aagccaccct ggccttttgt caaccaagg tccaggggcc aagcctgtga
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30061 gaaagtagct tcttcaaact caacagcaat ttgcatttgg agaaacccgg ctgtcagttc
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30181 acacacacac acacgaggtc cagcttcccg gctgtcagtt ctcgtgctga gcattcctga
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30421 tggccttagc tttagccatt caaaatagac aaagtctctt ttttcataat gtaaagaatc
30481 ccgagtatgt cgcagtaaca ggaataaatt ctacaacag aatatacaaa aacattgaat
30541 tttttttcat ctactgattt tcttttatat ataaacagag ggtttttttt tttaggaata
30601 atttatacac agaaagtatt tttatgtaac aaattggcca tattattatc ttttttagac
30661 tttttttttc tttttttaag aaaaaattta acaagaaaac tcagaaatgc attattggcg
30721 atgtgtccgc tccatcgagc cttttgactt ttgttttggt tttttaaatc ccagaggtag
30781 atgaactctg gcaaaactct tacttcaacc tcaactggcat aggaagcaga caggggttgt
30841 caccaggcag gcacctactc cacctgtaca tgtgtctgca cactgcccc aacccacaag
30901 aaactgaaag accaaaccaa accacaaat ggttcccaga cttttttcct gcagtgttag
30961 aaagtcccat gtgttttcaa caacggtatc ttgtggaacc agagagacat ggccaataat
31021 gcacggggag ccaaaggaca tggatcttaa tttgaaaaaa gggggcgagg ggacacacat

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FIGURE 6M

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31081 tgtgggttttt gttaccagtt tgttctgtat tagaaaacaa tggaccttcg gcgttcgcc
31141 ttagatacag gtaggcacag cattcgtag gatctgaggc acatgtgccc acgggctgca
31201 catcagagtc atgtgatcac tgtgaagcca ttccagtgtc ctgaaacctt cccatctcca
31261 tagtggttga gagctaggac cagccatacc agccagatgt caccatggag tgccatctct
31321 ttgctgggtg gccacacact gctatttcca tggccagcag ttctttccat ctggttgggc
31381 tgctacactc cacaggggaac agtgagtccc agataattcc tttccccagc aaagggttcc
31441 aagatcaaga tactgaagaa tacagaagta ctttttaaac cactggcatt ccttttgttt
31501 tgtttttatt tttatctgtt ttattttttt ttgttttatt tatttattat ttattttttt
31561 acaaactaga gcagaaagca tgtgggaaag aggggtgaacc acaattgggtc ctggggagaa
31621 tttcttttta attaattttt ttaagttttt attttttatt tttggcatat tgtaaagcta
31681 gctagtaaac aagtgtcaaa aaagaaaaag gaaacaaaga gggggaaaaa agaccacaaa
31741 cacatatatt tgccacacac gagagaaaaa aaaagtgttt ttaaatattt ttcggcaatt
31801 ataaactaca aacattttat aaaattatct tatgttctta caaaaatgca atgaaacatt
31861 gaattagttc ttgtaaacca gagcttcgtc aacgactacc cgtaatctac tggacttaga
31921 agccctattg aaaggataat gagtaattta aagaatgggt tactggaaag atgcagacac
31981 aaatgtggac acacaaatca gtgattatga agttctcaca gaaacccaaa tcaaatcaat
32041 ccctaacgtc atgccccaga ccgacaactc atctgatgag tgtgatggag tctgagtcct
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32341 caaggaatgt tcgtttctct aaatcgccaa ctgggtcatc aagctggaag cccaaagcaa
32401 agaccctctg cctgtccaag gtctgtatct tcagcatctc tggcaagaga gggtcaattt
32461 tacacagaca tcctgtcttg aagttctcat ttgtaccacc acctagtcca aagtggactg
32521 ttaaaagttt gaccatcatc actggttctt aaggggtgga tctctctggt ccagggtctcc
32581 caatgcagct gcttagccca ggaaatgaaa agacatcaga caaacataaa agtaacatta
32641 aaaaacaaaa ccaaagggaa aaaaaaaatc ccaaaccgta aattcattac tgctaaaatg
32701 ggccaaagca ttttgatgga gtggctctgt ctccctctgg atgccagtgt ttaggaaagg
32761 agatgctttc agcactctgt ggccactctc agaggacca acgatgacaa cagagggcct
32821 tgggtaagca tcctagactc ctcccccaca tgagctcagt gtgacctgc caccactgct
32881 tgcttacctc aggcacaggc actgccaaaa gaggtgggct gctaaggccg aggtccggg
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33241 tcagctctat ctccacgcct caggaagggc tgtgtggggg cacacctgga tgttcacgtc
33301 acctgcatgc tgtgcctcag tggttcatgt gacttcaagc agtgtgagct cctatcagaa
33361 ggggggggtg ggtgggggtg ggctcagagt aaaaaggcca cgactcagct tggtaggagt

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FIGURE 6N



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33421 acttgaagct tgtaaagaga aaaatcagga agaggcgggg aacatcagca tgagatcagg
33481 ctagaactgt ggatatgatg ctttgcaata gtcggggcgc gtcagtccag cagaacgact
33541 gcaccctcgt acaagccaac cttttctttt tattgaagtg tttctggagc attagtttat
33601 gacggccact acgctgttgg tgccgtctct ctacttaaag gaaaaaaaaa aataacaccc
33661 acgcaaaaac aaaacaccaa caactcgac agtttcaaaa ataataataa taaggaaaaa
33721 aaaaaaccct taaaatcaat tgaatgaact gtagaaatcc agttgtggaa aaccggcagg
33781 tatgtgcgag aggataggcc actatcccag agtgtcacct acagtgtaga agaaaaccct
33841 gatcaaacag tatctcccag tgaccctgtg agcatctagg aaccagaga agggcagcat
33901 tccagcagga ggcgaagggc tcctgagctt aaccgaactg ttaggcagtt tctccatact
33961 gggggaaaag attagccacc gcggtcccca gctgaagtcc ccagggcctg taagagcagc
34021 tgctggagtt gaggattgca ctgtccacct gtgagcagca gacggatggg tggacagagg
34081 cagagcacgg ggaaggctag gcgccaacca ctggccttcc agcctcaaga tttggtcagt
34141 ccttgtttag ccctgggggt tgcggggggg gggggggaag ggaggggaag agagggagg
34201 acagcagcct gcagggggca caggcttcgt cttgccccct tttttatact ggccttctgt
34261 cagaagcaga agggggagct ccctgaccgc tgtacctcca agaggaacca atgccaggag
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34441 cctgccctca aaacctggga gtacctgtc tcttagggat agaatttgtc agtcattcaa
34501 tctgtagaga aagttctgtt ccaaagtcag ccagctgagg atgggcccgg gagccccct
34561 ccttggttgc cctgtgtcca tgggttgaaa agtaggggac aggtggagg
34621 gaaagaccag agttgcccta ggaaaagtg gcttttgagg acagagcagg aagaggctgc
34681 tcatttgagt tagcgttgct ttaacccag aatccagcct ggccccctct tgcttcacct
34741 gggatatgtg cctgcggagt ggctgaggt accaggatca ttggcctact gtcagg tact
34801 gagaagtgtg agatgtatta tatatatata tatatatgtg atatatatat atgcacacac
34861 acacatgaaa aacaagagt aggtagataa atgtttgaaa aacaagcccc cccaaaaaaa
34921 ccccccaaaa ctgtcccatc taatacacac atacacagag atacatgtac cctttcctca
34981 gcatttaaat ccataacagg ggcttttcta cagtgattaa aacaggatc acaaaataaa
35041 ttaaaactcc tacatgaaat acctctttaa taagcttccc cctcctttt cctttaagg
35101 gcagaggcta ggaagagcca caagcctgaa cctacagaca agccagacaa ctccagcttt
35161 ccttcctgca tctaactctc agtcacaact gcaaccatca tcatccaaca gttttcctac
35221 tcctaattta aatatttcca ccagaaagca tctctcgcg tgctactgct ctggtaaagaa
35281 gtgctaaatc gaaacaagac aggaccctc ccccaacccc actccagggg gaggggcctc
35341 caagcccaga gctccgggat tctgggttaag gaggaacagc aaggggctct agggccactg
35401 tagggtcagc tctactccac tttgggattt ccggcccggg agtgggcttt atagcacacc
35461 cactaaagtt gctgtcctg gccatgggga gttggtgtct tacatcttgc tcccagggag
35521 gccaccctt cagacaagct ggttctaaag acaggtgggc ctgcttgtga aggaggtggc
35581 agatgggcca ctggaccagc tctgtgtcat cctggggact cagcagctat tgtgtgtgtg
35641 tgtgtgtgtg tgaaagatca aatattcatt taaataataa tccaatgact attgtctgca
35701 gttaaaactg ctattgtatt cccaaattgg ggtgtgtgtg tgtgtgtgtg tgtgtgtgtg

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FIGURE 60

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35761 tgtgtgtgtg tgtgaaccaa agcaaggaga gaaagcaaag tgtgactttc aacaacaggg
35821 actagaaaca ctaaaccagg atgtgtggga tttttaacct ttttgtttct gacctgagtt
35881 tgtggcatgc cttgccctgg agcagatgct gtgtgctggg aagcaaggaa aggagagagt
35941 agggcccagg agtctgtggg ctctggactc ccacctccc cactccctca cctgtgactg
36001 tgctcacaga gcctatgggt tagagggtaa tgaatggggc tgcagggagc aggggaaggg
36061 agatgtattt ataaaaaagg catcaaacag ttcacggcaa gttatgtcct agaagcatca
36121 gttgccggag aagaggaaga aaaaccacac tctagtata agcagaggaa gtttcttgga
36181 gtgagcagaa aggaagaagg ggtagacctg aaagtttcat agattaaatc cacaaagata
36241 aagaacaaaa aaaaaatagc agcttttctt ttctgtata gatgtataga tgaatatctg
36301 aactgtaaaa aagttataaa actgacatta aagacgatgt gtatgcaa atgttcacgggt
36361 ctaacataga actgagagac ccatgaagaa gtcctagtaa cagaccatgt gaaagctcac
36421 actgcttgga tccactgcct gggcgggcgg ctccaggctg ctgtggctct gaatcccttc
36481 ctcgaacatc cataaccaac agccggcgcg agtccccgga accctttcga gtgtgtggcc
36541 ctcaggggag gggcaggagg gaggtcgggg agggggacga ggctggtgtg aggaccacct
36601 tgaccacaaa cctgaccttc aagcttgccc atggccactt cctccagaat tcttgggggtg
36661 ctgtgggtgg gggaggggtg gagaaccagt tctgctttcc ccttcttcaa ggaagggcag
36721 ttccatcttg tccagttctc ccaaacggta accatgcaac gagaccagg agatgtgggc
36781 tgggagagcc gggcacagtg gggggcctca gcacgtgtct ctcaa atgtt atcatcaacc
36841 agacaccatg gttcatccca cgctcttgga caaagggaaa tcagcgcagg gagtatatgc
36901 gtgtgagaaa aaccaaaccg aaacacggat ttgggcaaaa atggcagcgt gaaaaatgat
36961 agccacggat gaacaatggc ccttttaaat ttgggggtga ccttaaaaaa ggttaaaaaa
37021 aattccatct cagtgtgtga attttttttc tttttctttc cttttctttt ttttaaaaga
37081 cctacgggtg caggcagggt tatgctgggt gatgaggagc cccaggggca gccattaagt
37141 caatctgatt tttttttttt ttttaaaaaa gaaggcttcc cagatgggag ttcacaaaca
37201 tttttccact gtaaagcaga aaagagagaa aggagagcgt ggaagtggaa ggggagaggg
37261 cagagaggga aggcagagga gagaaaaagg cagagaacga agagactcaa ttctcgagtg
37321 tcctgttgct attaatgtgt gtcatttaagg ttgagagagg cccatgtcag ttaagggttc
37381 gggtaaaagg aataaaaaagc tgcttgcata ttgaaaaaag gaagggtcca aatgtgttta
37441 ctgcagagaa gccgtctccc gtgggcagca atggcaggtc tgaagatcca ctgagggtaca
37501 ggaggcttgt gaatagattg ttacaacctg ctctcccctc cccgcccccc cgcccaccga
37561 gtgggcgcac acacgttact gttggcgcgt gcttcggtgt gtccgaggat cagcaggctg
37621 aggactgggg cagaggcaag gccctctcgt tggcgcgtcc cccgttcatg tgagcgttaag
37681 gctgtctctc atcaaaactg gcgcggagaa cgagcacgcc agggcccggg ccattctcag
37741 ccttggtgtc tgagtgtctt tcaggcagag gcagggaggc tgaggaggcc gaagggtcca
37801 gtgggacgct ctccatgttc tcaggctcca tctccagctc ctctggctcg ggaggcttgt
37861 tctcctcgt gtagtagaag gagacctcct ggaagctggg ctccatctca tccttgatgc
37921 tgccgatgat ctccaggaag gagggccgca tcttgggggt atactgccag cacatgcgca
37981 taagttcaaa cctaaggagg tgatggggaa gaaaggaatg agctgccaga gagaccaga
38041 agaactgtac cacctctgca ctctctgctt cccatctgga tgctctggc atcctgccat
38101 gtatcttgcc cagaaccag gccagccac agtgccaagc ccagactcac ttcaagtctt

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FIGURE 6P

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38161 ggttcaccga ttccaccatg gacggttgta ttaatgatag cactgctaag agataaaacc
38221 cacttcctgt ctaagcacct cttctggcca cacattaacc agaagaggaa acctctctct
38281 ctcactaatg agaatacacag ctttcctgac aggcaccatt ctctgtatct cacaccaggg
38341 ctattttctaa gtttcttcct ggcaccaggg cgccccctggc agtgggcctg agggaggagg
38401 cggcaggggt gctagacaga cggagcacat atcccaagct tgctatctca cgccagcacc
38461 tgctcactga ggatgtccca tgaaggaaga tccctgtctt gaagatgtag gatgccagg
38521 agcagagttc taatagaaac ttcaagtcgg atgccaacga accaaggga gtcctaagca
38581 tcattttctt ctacaaacaa ggccaaggta aaaacagtat aaagcccatg acgtacctcc
38641 atcactccca caaggtcaca aacctttgca aagcttcctc gtcctcgaga gttacatggg
38701 ccagctggca cacaggacag aagagaaagg ctgctcatgc agccaccgtc ctgaccagca
38761 aaggcctggg agtagacagt ggaggagacc ctaagcaagt gaaggtgtgt attgctgaca
38821 cgtgcaaggc catgtcaagg accccaatgc cccagtccca tgggagtggc aaagtctacc
38881 ccagtgatgc ttgcttagag agatggtaaa gccttccctt gaggtccgag ttgcaagtgc
38941 tgacagtgtg tgcagaatat gtccactgtc acgtccttcc cctggaagtt tacagcctca
39001 agacggcttc cctgcagaga tggctaaacc tgctccatg ttcagctgta tataataatc
39061 ctgcttcctt gtttatctgc atgcagtaat ctgctctctt gttcaaatat atacgtaaaa
39121 catactgagc ttccagagcc cagtcacgc agtccccgtt tctctatacc caagtgcaca
39181 ctctttgttc attcccttga tgccctcgtc aagtcatagt tctgcaacc aggccatgca
39241 gtgaaccaca cctgggctct gacggatgga cagacacaca ggcccgcagc aaaacaagg
39301 cagggtggtc atgattctga gggaaagggg tacctagcag ctctcaatca caggcgtgtg
39361 agaccaaagc actctccacc tatgtcctc caggaaactg tgttttataa aaactcctgg
39421 ctcaacagac gctttactt aaaaccaca aatggaagtt cgaacatata ggaatctcaa
39481 agcaccctga acaggcttct aacattctac caggctgatc actgggccac caggacactt
39541 ctttacaaag caaataatcc cacaggggta aaggcgtgtg aaagcaacct attggtaggc
39601 atgaagttgc ctgtgcagag aaagccactc ttgccatctt ggccagcttc cttggactct
39661 gtaggatcaa gtcaggccag gtggaaggta gttatcttaa aactgaaaaa aggtgcattg
39721 gagatccacc tccaagaatt aagcactctg gaggcccagg gtgaagcaa ccaattacag
39781 cggagccagg tgcagcttgg agcctgttgt tagcggaatt gtaccagagc agagctgggt
39841 acacagcacc tgtggctgtt tctaagctcc tttgtaggct gagtagttga gacagcggct
39901 gtttagctag gaaccttaca atatttactg cctactcctc tggaggtaaa gaaaaatccc
39961 aattaagtgg ccaatgtctc gacggaggaa aacaaactgg accaaagacc aggctaacta
40021 ggtattctca ctggctctaa gtgactggtc ctagtggcac atgacaggtt gcaggtaggt
40081 actaaaagct ctaggcccgg gagtcacgtc agtccccgag agccagagat gtctctttac
40141 tccaatgatt acaacacatc ctcatgtgat gcataaggga aaagcaccaa ccacagcatt
40201 tgatcatttg tctgaagtca cacagggagt gagctggaac ggcgtgaggc tgtcagacaa
40261 tgcagcttta ctgtaagtaa ccatggctct gctagcagac ggcgctctcc cgactgtcta
40321 cagacagtca gatctcctga gccggcttgc tctggtagc tgctgcagaa gcttgttctc
40381 cccggteccc atcatttccc gaaggattaa tcggaatggg aagcagacac aaggagctta
40441 gctccgtggc caggctgcaa tttcctctct ggctgacagg cctagccctg aatagaaaag

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FIGURE 6Q

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40501 tgcaaccggg ggcaagaaca tgagatgtgt ctggcccca gccccgtggc caggggtggg
40561 ggggtggggct gaggaggtgc cacgggcagg gtagggatga ggtgacatca gtaaaaacaa
40621 gccatgtgat gcctctttta aatcatccca gagtcagccc ttccagggct gcccataaaa
40681 ggaagtcttt tttgctctgt gcgatttaag accttgtttt tttttgttt tgtttttttt
40741 aaatactctt tccacaagaa aactctccag tagactctgg gattaataag ctgataaaat
40801 gctccctcta aaaagcacac tttaaaacca ctggacagct ctgatgagct ggagccgcga
40861 tttacagaat atgtccctct gtgaaggtgc acacctatcc ctctagaagt gagtgtctatc
40921 ctgggggtgt cgcccaccgc tatgccatt cctcacttgg cttctgagcc cccaagcaca
40981 ccccgtgtct tcagctggac aggtgccat ctatgtgagg cactggcaaa ctgaaatatg
41041 cccaggacct catgtataca gtacccttgc tgccgcctgt tagtactgta ccaggtagta
41101 gtgactctta gcagggatca gactttcaga agggcctacg ggactgagtg ggttctcttc
41161 tagaactctc agcaactaag gttgttttag ggccaggacc tagacgggga tgctatatag
41221 cccagttgct ggcacacagt cgatgccagg gaccgtccag cagacactgt cacctgcctg
41281 tgatgactct attcaattta tctcgacaaa accagactgg gattcccagc ctctgggggg
41341 tggagaggaa aagtacagaa gtagtcagat tggactgagt atgtctcagc tgcactctgag
41401 ctggtgacgc tcggctagta aaacgttcaa gtctcttctt gaatcccgca tcccgaagac
41461 ttggcatgtg agctctggag atgttaatgg atcaaatgga tcaattctgt ggctgagctt
41521 acatcgctct cccattctgc agcacgagg ctggaaacct tttcaggatc tccaggttcc
41581 gtgaactctg ggactggccc gtgacctcac cagggttcac tgacaaatct ggtgccaaag
41641 ccctgaaacc caggggtaaa gatgggaatg ataggctccc ctgaccagc ctcacagaat
41701 ttgctagatc aattcaaaact gagctattgc actgacagtc agacctggat accctggtgt
41761 ttggtggcag cttttcctct aaagctagaa cactttgtaa tacacaaggc tggatactta
41821 gctactcctg aagcagactg gttcatgtgt agggacgacg agaccaaagc atggccagag
41881 aaagggctgt tctgcctca gaaccacacc atggaagtcc ttcctctacg tgtgagaccc
41941 aacaggcttc agactactcc caagagtgtt tgcttactgt gccaaaaaaa aaaaaaaaaa
42001 atcctttcac agaacacatc ttcctctcct cagcgtctca gccaaatcag ggcaccacac
42061 tccctactgg agcagcccgg ctcctctccc ttcactctgt tcttttctta gaaaggagac
42121 cgatctgcca aggggttctt gaatggcaaa gcaaaaaggc ctcctgaatc aatcatttctg
42181 catccaagag cggcctccgt gtgtaagctt cctcctctct atgctgggaa caggaagtcc
42241 actgcctttc ccatagcagg tggctccttc ccaagcatat taaattcata ccaaaaaaaa
42301 aaaaaaaaaa ccaggcagct ggggatggat caacttcagg agttccatga gtttctcaga
42361 caaatgtttg ctccagcata aaagaaaaga aaaaaacca caatacctct cctgtgacca
42421 ggcccaaacc acaggaacaa aactcacacc tgctcttttg aacggtttct cagctcgtga
42481 gacagtgtct atcctggat cctaaccaag gctgggtggg cacaccctta cacagactca
42541 gaggcagcca tgctcctact ccatectttc acctttgccc acatactgac tattctcgca
42601 atggacgagt aggactgccc tgcaccactg aggtcaaagt aaagctataa cagcactcag
42661 aaccagagc ttctctaggc agggcccctg catcctgtac gccttcggag gtcagtttag
42721 aaaggccaca gtggcagtgt tctccgtgaa gatgctgcag ggcacagcag gccacggacc
42781 agtcagtggc tcaatatggc ctgctgtcta ttcagttttg taaggccctc ccaagcaaga

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FIGURE 6R

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42841 ggggttttttt tttttacact tgccaacagc tgggggcaaaa acaaacaaat taacaagtc
42901 cccacgcccc acccccaaat aggagtattt tataagaaga aaacgagagg aattcaaatt
42961 ccaatataaa gtttttagttg ggcaccagca gtaacactgg ctgcaatcca agcactaggg
43021 gagtttgagg caggaagatt atcctaaata cctggggtac actgactcca tccttggtga
43081 ttcctgaatc atagtggcag agcagagggg ctggaaggaa gagtgagcgt gcggtcccca
43141 gcaccaccaa tcctctccag tgtattagag aaatcctctc agtctatgga gtggtccaca
43201 gagaagccac ggcctctccc actacacaga accatcactg ttcctaccgc cctgtagtaa
43261 atccgatctc cttacaatca cccacgtac cggagtatct tcatctgcgg gaagccctgc
43321 ctctgaccag cagctatctt ctggagaccc tgagctagct agtgtcacct catcgagctc
43381 ctcctagggt tcattagaaa gcctgtgaga tgacattttc aactgttgga gcctcacggg
43441 ggacgatgct agccacaccc ttgacatctc aagattcaga gtacagtcac tagcacctct
43501 ctgtgctctg cccaccacct gcactgcacg cccaacctct ccatctgtac attgcctcac
43561 catecaaggc gccacgagag tgagcgctgc gctggggaag agaaggccag gggtaggcag
43621 agtcttttgt gtagaagtga agaaatcttg acaaccccc tgggattctt tcaactagtg
43681 agctgaacct gttttgaagt gtttctggga aactgtatgg gtcctgacat atcagtggga
43741 acctgctttg atgcttaacc ccgagatgca gagcaacagc cgagccccac cttaacgtgt
43801 gcacatcaaa tgcaagtcca ctgctctcaa cctgtactcg atgagccaat cggaatacct
43861 tcatgtcttc cttgaaacct cactccaaga agtgccattc tcggggctgg agagatggct
43921 cagcgggtaa gagcactgac tgctcttctg aaggtcctga gttcaaattc cggcaaccac
43981 atgggtggctc acaaccatcc ttaatgagat ctgacgcctt cttctgggtgc tgtctgaaga
44041 cagctacagt gtacttagat ttaataatga ataaatcttt agggcagagt gagtggggcc
44101 gaccggagtg ggcaaccttt gttcccagca accacattaa ggctcacaac catcagtaca
44161 gctacagtgt actcatatac ataaaaataa taaatctttt aaaaaaaaaa aaaagaagtg
44221 tcattctcca gacccactga gccaccaaca tcagatgaca aagaaagacc tctactcaag
44281 agagtacaaa taaaaggccc acatgtggaa agattcttcc ccaatttttg caacaccagg
44341 taacttctga ggggtggagc ctaggaggct gccaggtcat tagaaagtta tcttcaagat
44401 ttaggactac agcaggaaga ttgtgaacct ctttaatgca ggggttctca accttcttaa
44461 tgctgtgtcc ctttgacaca gttcctcatg tcgttgtgac ccccaactat aacactactt
44521 tataattgta atctgctact gttatgaggc aaaatggaaa catctgtgct ttctaacggt
44581 ctccaggtaac tcctgtgaag gggcaagggg tcacgactca caggtagaga acggcttctc
44641 taatggctcc ctttcacttt caagccacaa agtgagactg tgcgctctga cacacctttt
44701 ctaccgtaac agttacctcg ccacaaatcc aatggacccc actgccgctc ccacactggg
44761 agccaatgtg aaatgcttct ccttgaagc tgtttatctc agggagtttc tcgagtcaca
44821 ctggctgagc acggagggtg acgtgacacc acgtgtgtac tgccatcgag tgacaattct
44881 cacaaccaat cgatgcagga tgttattttt aacagaagtg gagcgaggca accatctcac
44941 caaccccccc taggggtgtc ctacaagcat gtccaaagag ggatgagctc aaccgtgctg
45001 taggtccatg cagctcgaag ggattaagaa gacagcagat ggtctgtgac cttgtgtgtg
45061 ggctctctga gctttagtct acccgtgcaa gagagtgaact cctgaccaca gagctctgtg
45121 tgagcatgct gtatagacct tccaggggct tggggagagc tttcaaattc ggctcagcag
45181 tagtaactaa cttgcatttt tgtcttaaaa attaaatttt gcatgaaaaa gatgagccag

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**FIGURE 6S**

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45241 gattgctcat gtatttcaga gatgggagat gggggggggg gggtagtggt ggctgagacg
45301 cagcccatgg tgcaaatgac caattagcac tgggggggacc aaggggggac aggatgagat
45361 taaggagcag cacaagtca cagatccaac aagctcagca gcagcaggat agagcctttc
45421 taatcctctc ctgtacccac acacaacgga gtgggtggct ctggaaatac atacagcata
45481 tcagggcagt tgtccggctt gtccagaagg ccacctcca tgacgaaacg aagaacttgc
45541 tcgttggaca agccctggta gggctgctca gccagcgtgg cgatctccca gaggacgacc
45601 ccgaaggacc tacaggtgga acagaacagg aacagctcag aaagggatgg gaaggggccat
45661 gtccctcctc tgccagcatt tcttagactc tgggtcctga aaaaaagtgt cctcaatgtg
45721 acgactgcac tttgtggaca tcaaaccagc cagcttgcta cgtgtgggac atctgttccc
45781 ctttgtcact gctaaggctt cctatagggc tactgcaacc cagggtgag gtaattaatg
45841 ttagggggctt ctaacatctc tcacagtttt aagagcccga tctacagcgg acacattcag
45901 tgtctggtcc cagccattac ttggacataa gccaaattag ctctagttca gcaagggaatg
45961 cagaggacca ggtcccagcc tggccactga cctgagacag ctaagcatct caactatctc
46021 ctgcagggat ttctttcatg ccagcttaga aatactgatg ctaatgggtc tccacgcctc
46081 cgcaagaaga atctgatcag ggttcttaaa acaatgggta tcttgggctc tccaaagcaa
46141 ttctgacctg ctggttgtag ggtagggagc tgggcctgga atgtctcaa gtctgttagg
46201 atcttgactt gggcaagga agatgaaaac tcgtcccctg cagaactcag gagccatggc
46261 tgcagaggtg gctgtgtcag gaaggggaact ggggtaggat acactggcca ggggtgtgtg
46321 cgcaataaca aagagtccct tggcttagag gctggctgag gtatgaactc atcaggcgaa
46381 gcagcgagga ttctactcgg tgaggtatgg cctgtcagcc cagaagatgg aactaaagga
46441 gatccatgca tgcagacact tcagacagac aatggtcaca ctgtcgctca gtgtgaacac
46501 accttctcag ggagaaccct tgctttcaca aaattcttcc tggcctgtct gctcttatgg
46561 tcaggctgta tggctagaat gaagaaggct gcccatggca agccaacaca aggcttcgga
46621 tggaaacctc gcagggctga gccccacaga agagcctgag gcggccattt tccacttagc
46681 actctgagga tcctggccta agctggagca acagcctctg actgcatctt aacttttggg
46741 tgcagcttc agtttcttc taggaacaaa agggttttgt cccaactgat gctaagcaat
46801 gtcagacagg aacagaacct cagcaatcag acccaagttc ctgggaacc ggcagtcact
46861 aagacagaca gtgcagttac ggttttcaaa gacctggccc tagagaagca ggtttcctgt
46921 gtgtttcagg cctgggttct gccttgacga gcctttgtgg aactcggag gcattcttta
46981 gaggctgcag tgctcaccct catgtctgaa tccggcctga gacaagcagt gatgtatgtg
47041 gttttctctt tttatcaacc ggtcttgacc aggttccctt ccaagccgac tcccctgtc
47101 tttcatgctt tccctgggtc accacaggct ttcaggcatt cagtcacaat cctggcccc
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47221 ctccagtgtc actcttgctg gcacctgtt ctcctcctgg actccctgca ggccaacttc
47281 ccattccatc ccaccccatc tcagcagcca gtctgctcat aggacggaca ggaagataga
47341 gagtataaat cagaaagaac gaagacgtgt aagggtggc cttcctgccc ttgtgagggg
47401 ggggacagtc cctgggacat ctccccagaa gctcaaataa cagctgtgat aaatgcagat
47461 ggtcaggggtg tggcttgacc tgaggacacc tcccctcacc atgttccctaa ggtctcctac
47521 caagtcaaac aaaatccttc caacttttct ttggattttt acctacttct gactgtgaat
47581 tcattctaaa atgactgcaa ttcctctagc aagcagaggt tcaggcagag ctgagcatcc

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FIGURE 6T

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47641 gtttatacgt tctagtgtcc ttgatgtccc cagctgtgtg ctcaaacacc ccagcacttg
47701 gcctttttctc ttcacgcatt ttcttattgg tttgtaatgg ctacgtaatc caagtggagg
47761 aaacctgcag gaagcaccct gtgcgcctct ggctgtggca tgcagttgtt acccagagtc
47821 ggggggagaat gagtctgtgc tcactcttcc cctatcctgt aaggatgatc ccaagcttcc
47881 agaaaaatga agcttagaac aaacagatgg aagtgtggcc ctagggtgtc cctctcctgc
47941 gacctcatct acacatggaa cagagtctct tgattcgaca gagaagatgt aacctcggag
48001 aggctaattg cagagcagac ctcatcctag agtcgggaaa caaccaggcc gcgctgggtc
48061 atattcaaag gctattttcca atttgcacct gtcttccaaa caagatccaa ggctcttgac
48121 cgggaaagggt tcacgaggct aaagaactga tgtcagtcac tactgagata gtttctctgt
48181 gtggtcatcc gccctttgaa taaaccaacc accgcttctt ctgtgacaca acagcaacgg
48241 gatctcccga ggagacagcc aagacacttg ctgacattcg aggaggggga cgacgtgcca
48301 ggggtcctgc ctgccaagaa ctccagttgt attttggaa cccgatgacct ccacacggtg
48361 tttccaagga actgcagtaa acattactac agagaagtct ttgcaccctc tggtcagttg
48421 gctactaccg caagacactt attattaagg aagatgcttt gggtcaggaa taatggacat
48481 cgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgaacaga
48541 tgagaccaac agaaaaccac aaccaccaag actcaagttt tgggtttaaa taaagcactg
48601 ccttcaatct gaaggtttctg tgagctgcgg caggagcaca tacataccca gtaccaactc
48661 actgagagtg gggaagagag acgggggaac aggcagaggc gaaggcattt ccccgctctt
48721 tggaaatata atcaatattt gctaaaaatg gaaggaaatg ttggttctac ctactccttg
48781 gcttcccaca gatacctttt ttgctttaat ggactccaca caggaatata taaaagacaa
48841 agggctaaac ggcactgaga gctgaactca aggcctggcag ttggtcacag tgaacaaaac
48901 aaggaggaga atgagccacg agtgagaagg tccaagctgg ccatggaggg aaactctcat
48961 accagacatc agaatgagta gtgaagacac catccttgag ggactcggga gacatccagc
49021 gcacaggcag caaccccttc ccgcctttcc ggtagtagtc cgtctcgtag atgtctcgtg
49081 tcataccgaa atctggaggg aagatgcaca gttactcggc tggaccagggt cttggggcag
49141 agccctgtcc ttcccccat attcaagggt agacatgttc ttgctccact ctgagagggc
49201 tctagcatca cagccacttc acaggagaat acaagacatc tctgggtctc atcaggctcc
49261 ttttaagaaat taactccctt ataacattta aagcgagagg cagtttgcaa aatcattgag
49321 taccatgatt tttcaagaaa atatacgccg cacagggtga ggatatagtt ttaaagtttg
49381 gtccaatata cgggaggatg aagaccccat ttacttggtg gtgtgtctct actgctgagg
49441 aaaaggcctt ttgccactcc acagaggaca atgtacgaag taagaactca ggaagataaa
49501 aggacagcaa acagctgaga tgttcttcac caggctcctg gagctactac ccaacaccct
49561 ttcccaacac aatactctca ctcagttttg aaaatgtttt ccattttctg agtttcatca
49621 tgggtgaatgg caggcttgct tttttataat ctcacattac tgtgtcttta tccatttttg
49681 attttccact caaccgcacc acctttccct cacataaact cttgcattct ccttccctgg
49741 aggaagagc tgctcaacct ttaaaatgtc ccctcgcacc tctaagtggg gccacaaaga
49801 ggtgaggtac aaaaaaggca gagcaaacc atgtagggtt tgctctgcat ggatgttaac
49861 ccaacacaat tgacttgac cgctgtctga gctactggct gcctctcttg aactgattta
49921 ggggtgtgtaa tccctgagat gggggcactg ggggacactg aggaatgcag aactcgcccc
49981 aggaggaaaa aggaagtgtc taaatctcat ctctgaatta atccagagac atgcaaatga

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FIGURE 6U

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50041 gaggatctgc tttgacttgc ataaaagggg aattctagaa aacaatctct ctccctaaat
50101 gcaaaaagaaa aatagaacaa cccctctctc ccaaacgggc acacacaatt taattctaaa
50161 aagaaaaaatc ataattataa tagaaaatat cctcataaat gcgccacatg gttaagcaga
50221 aaatataaatc cttactgatt tggatttaaa atggcaaaaa gcacacgcac acacaaaagc
50281 atttttccaa ctgtaatgca aaatgggacc aaagcagcct ctgggagttc ctggctgtgc
50341 tgagaaggggt gcacagcagg gtaagatgag gacaggggca caggcttgct gtcccagccc
50401 gcctcctcct ccagctctgt cccaatccac tctcactcca cagggtggga aagatggcac
50461 agggaggggaa ggcacctgcc tcaggccact caggagcaca gtttcctctg aggactaaaa
50521 tctagatccc cacacataag ggagggatgg gaggcaggaa ggaccacaaa ggctgggttaa
50581 gaggatgcgc ctcttatcta gaaactctgg ggcggggtat cctcttaagg gctgccacc
50641 aagctaggctc cccagggctc caaatatgag tgtacaaacc cagagacagg ctgggggtat
50701 cttcagttaac tccaatgact gacatctgtt ctgtaacaca gctgcagtgc aacacccta
50761 actcctgcaa tcagcaaaga agagagcccg actttggata cctctctaga gatgacacc
50821 atcgcttact aagaggccgg aatggctcat gcaaaaacca cttctagggt tgaggcaagc
50881 agaacatctc caggacacaa gctcaagagg cggccaaagg ttagtggtctg atcgctctg
50941 ctacatcgctc tgtccctctg cttgttctca ggatggacac ttgttatgtt tctgacctgc
51001 tggcctatcg cagtaggaag gtaaagtata tgcaggatgg tttctgagc aaccttggtta
51061 ctactttttt tttttttttt ttttgaagta aaagacaaaa aaacaaagcc aatatacaag
51121 ctgtaaggctc ggggagaatt tctagccaat gaccagagat gtaatgcaat cagtgtttta
51181 ggatcacaaat gtgttggcag caacaaggta ggctgagcag ctaaggctcat ggcaggaagc
51241 tatgcacgac agaacggcca agtgcttggg gctaccactg aaggatgcac ctcaagtggc
51301 taaccagcag catacatcag gccctcgggt caattcctgg cagcaggaga ggaggagaga
51361 acttagagcc gaccagtcct atgagtgaag agcagtcagc agtgatctcc cgcggaactga
51421 catgaccacc atataccctt cctgttacac tatgcagggt ttcaccatag gggcacctgg
51481 cctcttagga accccatggg cctattcagg gacaatgctc tttgtaagct gagaaacttg
51541 aggggtggac tggatgggtg cattctcctc aagccaaaac cacttcagga agcaagctgc
51601 cccgattatt tctgtaacgt ttgacctggg gagcagggcg ccaatctgga ctaccatggt
51661 aagggtgctc ccgggttaca gccaggaata gacagtcaca ccgactacat acatctttgc
51721 actcaagggc gaggcactgc tcctctcgga cataatgaaa atctctccag tggcagacta
51781 atgactgcaa agtccccctc gcacctgtga gttcagttta gcctgtgctc caatctggaa
51841 agcaaaggac acacctccaa ttttgactgt gaaatcttcg gctaccatgc agttcctagc
51901 agcaaggtct ctgtggacga acttgttggc attgaggtag gccatgccat ctgcaatctc
51961 tccagccatc tggatcatct tgcttaagct cggaggaatg aggactagat tattctgctg
52021 cagattcaaa acaagacaaa gccatgagca acggagacct ttcccccta acctcctgta
52081 ggtctacact aggagtctga aatgcatatt tacttagtct gagtaccaca ggtcacctgc
52141 agggagtcag gacttgctaa gaaggactag cacttctagg gaccagcaat ctcttttccc
52201 accccctccc atgcatgcat gtgcatggat gtgggggcct gaagcttatg ttgggagcta
52261 ccttctaccc actggttgag gcagggtgtc cctatcaaac ccaacctggg caacatagat
52321 tgctctgggg atcccaactc atccttccaa ggctggaatc acaggtgtgc tgccacacca
52381 gccagcctt tacctggctt ctgacgacct gaactctggt ccttatgcct gtgaccacc

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FIGURE 6V



52441	cctccccct	agtcttttct	atttgagca	ggacaaaaat	gatttgaagt	gaatcagcaa
52501	gttttagcat	taagcattct	cagctccagc	tagtttccat	gttccttttg	cttccgccat
52561	caccaagtgt	gagtaagagg	aaggacagag	aaccctgaca	aaggccacgt	gaaacagaca
52621	cacttcctaa	gtggattacc	acgagctttg	cttcccgtgc	aagctgccag	gacttattcg
52681	tcttcattcc	cttcttctaa	ggtacaaaga	taggaagact	aatgctttcc	tcttggtatta
52741	ctgttttcta	cgggcactga	ggataaccac	agttcaggtg	gagttcacct	tggaggggac
52801	caaggacact	gagcagcaat	gaggaccaat	atcatgtctg	aagaggaggg	caagatgctg
52861	ccttaggaac	tgaaaagaat	taacctaaaga	agtggtaaaa	tcataaacia	acaaacaaac
52921	aaacaaaata	agataagatt	tatgtctaa	aggctgatga	gaatggctta	gtgggaaagg
52981	tacctgctgt	caagacaggg	ggcctatgtt	catgtcccaa	gacaggtagt	gtaaaagatg
53041	aaaaccaact	ccctcaaggt	ctaagtaggt	atgcacatgc	atatgcatga	acacacacac
53101	acacacacac	acacacacac	actacacaca	tacaaacata	aaaaattccc	aaaggtccgt
53161	cacccactc	ccatgtgcaa	aaccaacat	gacccttatg	cctcagtttc	cctaactgaa
53221	aaccttctca	tacaacacta	tgaagccatc	tcatttctca	atgtatctca	agtcacagga
53281	gagcatgacc	aggcttgagg	atcacactat	ttgggctagt	atataggccc	tttgtgtctt
53341	gaccacgatg	aacactcaag	agcattctgg	ctcttggtcca	gggttgctaa	gttctcagca
53401	gatgccagac	tctaggaggc	cagcaacagc	cctctagcac	gtccaggagt	actctccaga
53461	cgacatggca	tgtgaggacc	aagttgagct	catttatcta	tttaaccatt	ttcactctga
53521	tccagggtct	cttctataaa	tctaggggat	gtcctcagag	gatgtgccat	cacagtgctt
53581	tccttgtcac	gctgaccttt	agcaccggtt	gggtcttaca	tacacatggc	aaagcaggac
53641	ctctgcagtt	ccgtgacatg	tacttatagg	ctcatgacac	atactgcagt	gtatgtgtgt
53701	aatgttgtgt	aactgttcaa	caaagagctg	tcacttaaca	tgtgaaaaac	aaccaacaat
53761	ggggacttaa	ttatgtgcag	gaaagggctg	ggctgacatt	ttgtcagttc	atggtaatat
53821	gttgtcattc	ttttcttcat	ctcgagaaag	aagaaatctt	tagttttgtt	agagcctctt
53881	aaggtgagca	cacatccata	cacttatcta	agtaaataag	caaacagcaa	tggggggagg
53941	tagaatacgc	tgaagccggg	gtgtatacac	tgaagctggg	tatatatact	ggagctaggg
54001	tatatacact	gaactgtgga	gtatacattg	atgctaagat	atatgtaagt	tattttttaa
54061	aaaattctga	catgagttag	acaaaattta	gatctgatga	atttaaagat	taagttttac
54121	ttccgaaaga	gactttcgta	atccaacctg	tctctttaca	ttgaattaaa	attttgtttt
54181	atgtttgtgg	gtgttttgcc	tgcattgtgtg	tttgtgcaat	acctgcccac	ggaggcccat
54241	ggaggccagc	agaacagtga	ataccgacag	ttatgagccg	ccacgtgggt	gctgggaatc
54301	caccaggggt	tctttggaag	agcagccagt	gctcttaact	gctgagccat	ctctatagcc
54361	ctttctctct	ctacatgagg	aagcggaggc	ccagaggcat	ctgttaactg	aggactggag
54421	gtaaccaatg	gcaaaaacag	ccccgagagc	acaagttacg	gggtttactct	gggcattgtg
54481	caaaggcatt	aagcacattc	tgatgttagg	agggtgcctta	aaggaccact	ctccagtctc
54541	cttctgtaga	ctgggtatta	ctggggtagg	atgctgctgc	tgggagaaac	aggcatagct
54601	ttgtggctct	gctatcaatg	catacaccgc	cttgtggctc	tctcctgaaa	cttcagaaac
54661	acacatgagg	acattttgtg	acagggtactc	agaactaaaa	tgaagggaacc	atccatcact
54721	tggtagatga	ttacgttgtg	gaggaaaaga	aaacgaaagc	ttctacagag	aaggggagca
54781	aaccagaaa	gggcccagga	agaggaagtt	ccccttacag	cgaatgcaga	gacaagctgc

FIGURE 6W

54841	ttagttagcc	acaggtatca	aagccagggc	cgaagtgaga	gcctcagagc	ctgaggcagc
54901	cccatgaaag	gcatttggtc	cagcaatatt	tctcaacacc	cccatcagtt	aactccttagt
54961	gaggacttag	aagccaaact	taagccaggt	gcttgtgggtg	cataccttta	atgccagcac
55021	ttgggagaca	gaggcaagcg	aatctctgag	agttcgagggc	cagcctggtc	tacgaagcga
55081	gttccaggac	agccggggct	gcacagaaaa	aaaaacaaaa	caaaatgctg	tctcaaaaaa
55141	caacaaacaa	acaaacacaa	aaataacaa	aacaaaaaag	aagtcagact	cacatatgct
55201	aaaaagctgg	ctgtgggcta	acacaacaga	aggggacact	ccacagtgc	taatcaaaaa
55261	attacacagg	acctactcag	gttcacagtt	tgaaaatctc	actagcctta	agcagaatca
55321	tgcagctgga	atgggttatca	tttaaaagcg	caggcacaat	actggcttat	tgcctagcct
55381	ggggagtagg	ttcagggttt	gagaagtgtc	tgaagcagtg	tcggggcaag	gggagagcag
55441	tgtgtgccat	caaggtaagg	atagcatgct	cacatgtaca	cgtgtgtgtg	tgtgtgtgtg
55501	tgtgtgtgtg	tgtgtgtgtg	tgtgtgtgtg	tgtgtgtgtg	agtgtgtgtg	tgtgtgtgtg
55561	tgtgtgtgtg	tgtgtgtgtg	tgtgtgtgtg	tgtgtgtgtg	acagtgtgtg	cgtgtgtgtg
55621	ccgggctgcg	agtcactctg	gccaaaacct	ctgacaacct	gaagagtgc	ctttattgag
55681	tacttactga	aaaggttacc	agccacggtc	atgacctga	ggtaagaag	aggtcaccc
55741	cgaggacctc	gagagtaaac	gtatgctagg	cagtcaagt	tactggaaag	tcagtggggg
55801	agggcagccc	ggcctgagtg	ggaagctgtg	ggaaggggtg	gccatgacac	gtggtagagc
55861	agctgggggt	ggtgtaagat	gtaggcaggg	gtagcgggga	tgcagaaaca	agagcacaga
55921	gatgtctggg	gttgaatggg	tgggtgcag	agacagacct	tccaaagatc	ccagtctgcc
55981	tacacttggg	caatcctata	tagagggaac	tgacaagaaa	gcatatctca	aggcactcaa
56041	ggctgagaag	caaatggact	taaagacacg	tttctacaa	gccagctcct	gaaaaaagt
56101	gaccaagcaa	gataacacag	cgaggaacaa	aactgacctc	cacttctggc	ctcagagacc
56161	ggagataact	tttgagatca	ccgcgtgtca	ttagttccat	gatgaccagg	gtgggtggc
56221	cttgggatac	cacacccagc	aaccggacct	ggaggaatca	agaaaaggac	tcagaggggg
56281	aggggggcat	cccacatgat	gacctacgcc	tctcggaact	gggtggtgct	ggggcctgta
56341	gccaggagca	gagttctggt	gggagggcga	gggcgaggct	cccacctcaa	gggtctgtgg
56401	gtggcaagaa	tgcaacgggg	aaactaccca	ctgggaagag	ggcaaggcaa	caattcgtag
56461	ctggccaagg	acatacaggg	tggtcctttc	tgtccatact	ttctgtccat	gtctcatctt
56521	ggcttcttac	cacatggtga	caattgaact	ccttcatcac	cgaggcctcg	ttgagaaact
56581	cgattctttc	acgcatactt	gcagcctcgt	ttaccgtctt	gatggccact	ctggtttcgg
56641	gttcatcctt	gaccacaccc	ttggccactc	cttcatagac	catcccaaag	gacccttgtc
56701	cgagctcccc	gttcatggtg	atcttctctc	gagctacctc	ccattcatca	ggcacgtaca
56761	ctagtaacag	acaggatgga	aacggccctt	agacagagat	tacaagatgc	tgtccctaa
56821	gaccaccaa	ggagaacatc	aaggtacaaa	cagtcacgca	cgggtactca	atctctgagg
56881	actccatgac	actttgaggg	tggtactcgt	agctaagaac	cagaaggaaa	ccaagaaacc
56941	taagatagga	aaaccaaata	aaaccaaata	acagtgggtc	ctttttcata	tccttggcaa
57001	aaccccaacc	caacaaaata	aaaaaagcaa	attagcccta	agagacaaag	aaagtgggac
57061	ttctgttttg	cctgtcttca	tcaagggatg	gaaatgtagg	tcagaagggg	agaacagtgg
57121	gaggggaaa	gaccaaaggg	ggtcaaactc	cctcctccct	ggatgaagcc	agaggtgaga
57181	aacatcctct	gcatggcctg	ggtgccagtt	tacaggccac	ccagcccccac	tgtaggcctt

FIGURE 6X

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57241 cagcgccttga agtcgtgctg gaagtaagac atatactgca ttttaaagac ttgcttaaaa
57301 caagtaaaaa aagataactt ttaaaagatt ttaaaattta cgtatacatg tgaaaatctc
57361 tctctctctc tctctctctc tctctctctc tctctctgtg tgtgtgtgtg tgtgtgtgtg
57421 tgagcacaca cacatgcaca gatgtgaggc accaccgtg tttgggtgcc tgggaaaccc
57481 agaagacagt gttggcttct cggacctata gttacagatg gcgggaggtc tcttcacaga
57541 ggtgctggga actgaattag agttctccag aaggctcagca aggctctcaa ctgctgggcc
57601 catttttttt tccagctttg tattccaaag acttggttaa agcaagtta aaaagatagc
57661 ttttatatta actgttggat gttgtgggct aaatgaaaat tctaacagat ttatctcatc
57721 agctttttaca cttaaaaaaa catggctact agctgggtgt ggcaacagga aactgcagtc
57781 ccaccccgag ccactgggca tggaggttgg agatggggtc tgctgaacta aaggcatctt
57841 cagatttgtg ttcaaaacac caagacaatg tgcagccgc ctgggatgtc tatcagttca
57901 gcacttcat tccacttctt ccatagcaat gtccgacaac aagctcaagg tggctgagag
57961 ggagaaactc agtcaacact aaaggcagag actcaagaga agagtctctc gccatcaaaa
58021 gaaaccgcag aaaaggagat gagaggccag cccccacccc cacccccgcg gagcgtgag
58081 gtaggtcttg tgcactacaa gcactgtctc cctatatccc tccatacagc tgtttaactc
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58201 agtgacgata cagactgcct gcctttttcca cctgagagga aggagaactc acacgttgat
58261 gaagaaaaaa gcagggttgg gagatgaaac ccagggttca aatcccagat gattcaagggt
58321 gctctacagg ctgtaaaatg cagtttaatc ccagggtctg gctgtgttgt ttttcaagtg
58381 atttgactta gtggaatgca tactgtttta aaaccatcaa ttttgtgaat ggctgttttc
58441 cctgcatgca tctgcactgt acgcacatag cacctgggtg ccactggcac gtgggttctg
58501 ggaatcaaat cagggtcctt ctagaaaagc agccagtgtg ttttaactgct gagccatctc
58561 tctagccccg gaatgcatga aagtattaaa acttaacaca agaagccaaa ctcttgcta
58621 acacaggtga agcctaggag cccctttcca ggggatctct agtgagggaa gtgagcgtg
58681 ggatggaggg ggactcagta gtgacccac ggctttggcc tgcactctgc aatgccagga
58741 acctccctga cacggacctg aacagaattc cttctccagc ttccattttt gggtatgctt
58801 gatctgggtt gagaaaaata aataaacgaa tagttctcag aaggaagggg gaagagaagg
58861 aaagaaaata agagaggcaa gtaagaaaga ccaaacacag gctccatccc ataacgccag
58921 tgggtacagc gagaactgaa atcatatcaa attaatcgt aagatctgga aagagaatac
58981 ctgctccatg agaaccataa cctaacagag ttactgacag ccctgtctaa cagaggatgg
59041 ccagcaggca tggcaagaag gaagccctag cttagagaca ggcctgggag gggaatcacg
59101 gctgtgtttg tttttatgct tttagatgcc gagctgcagt tggaggtggg agacccacc
59161 agcaggtcat cacggttatc agtcaccctc agagcacaag ccttacttc taagtatgt
59221 ctttaagggaa ggggtgttat tataaattcg gggctgggga cccattgac ttgtattttg
59281 aagaatggaa catacatctt gtggtgtgtt gaataggagt ggccccaca gactcacaca
59341 tttgaatgct tggtcattag ggagcagtga tacctgacag agattaggag gtgtggcctt
59401 gttggaggaa gtgtggcacc gaggggtgggc tttgaggttt caaataccag gcctatgtct
59461 tgctctatct ttgctgcctg atccagatgt agaactctta acccctctcc agcaccatag
59521 caccatgtct gcctacatac catcatgttt gctaccatta caacatgggc ctaaaccctt
59581 gaacctgtaa gtccttttaa gccagccact ttccatgaga agagctgctg tggtaacgg

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**FIGURE 6Y**

59641	tgtctcttca	cagcagcaga	acactaagac	acatacttat	ctgtctactc	acttactctt
59701	acttactggc	tgatttgggg	acaggactgc	tctatcttgt	tcataacttg	cttgaacttg
59761	ctatgtaatc	caagctagcc	ctgaattgac	aacttttctg	cctcagtgtc	cccagtagct
59821	ggattccagg	tttgtgtggc	cacatttggc	tctgtgtgat	gtttttgtat	ttcatggaa
59881	atgtatgtct	ggtaatttct	caactagaat	tctgtcttcc	atgggctca	gacaacttgt
59941	gaccctgcag	aggctgagct	tgctgaggag	agcagagggg	gaaaggctt	tataacacct
60001	ctctgtaagg	atggggacca	ctgtctccat	ttattacctc	taaggatcca	ggctggcttt
60061	taatgagaat	caactacacg	gcttgcttgc	tgcagagcat	ggagftaaaa	gcccatacaca
60121	tccattccct	gggaggcccc	tgaagttagt	ggtctcaacc	ctttttctaa	actcaatcca
60181	gctgccgact	ttagccagag	tacctcagct	ttgccagcca	gagctgttca	taaacttcgt
60241	acaatgttat	cagcactttc	ctgtagggca	ttctcagtgc	actcttgaca	acagcaacat
60301	gcagattaac	tctgggagaa	agactgtttt	aaagcacctt	tcagatgcaa	tgctactttg
60361	tagctctttg	aggcaaaagg	cttgtgtctg	tgctgtgctt	gtcaaaaggc	caaacaacc
60421	aagtgcagat	gaggtgacag	tgttctcacc	tggtgacctg	ggtagtgaca	agtttgttct
60481	tgctttgttt	tgaagggggg	agggagacta	tttctctggc	acctcttttc	tcttttataa
60541	ttattgacct	agacacaatg	gctgcacggt	tctggctagt	taggggacgg	aggcaagggtg
60601	ttcagatcat	ctgaggccag	gagtttgagg	ctggcctgta	taaacaatgc	atatttagtt
60661	tcttgatatt	tgcccgtttg	ctttcttgtt	tgttttggtg	gtgtgaggac	agaaccggtt
60721	ctggaacacc	gtaggcaaat	gctcttcac	taaaactacat	atccaaactc	acttactttg
60781	tttgtttgtt	tttaggagaa	agatagtctc	cgtaagtaac	tatgtaacta	tgctttcaag
60841	tgtggtgctt	acccttctag	tgtattttct	atgctttata	ggcacaacag	tatgcacata
60901	tgccacttta	aaaaataact	ctgcaagacc	ttttgcaaac	agaaataaca	tcattattct
60961	gcacctgatt	caaattcaga	agaggctggt	cttgactggc	tttactatac	acataatcca
61021	gttataaatg	attaaagaaa	ccatagtaaa	accatacgca	cttacatggg	gcttttaaat
61081	tacaaagggg	tttctctttt	tttttttttt	cccatgtgag	caggataatc	aatcggactg
61141	tgtctttatct	gggccgcac	tacttacact	tctggagcaa	agaaacattc	ctcctgaaca
61201	aactcctgcg	ctgcacagac	ccccacttaa	ccagattccc	tacatagccc	agcaacctca
61261	cagctagctc	ttccatacac	cacatcatga	ggattcagga	ggaaggcttg	ggatgtccct
61321	tgtgcagact	ttccacggct	cagctgtggg	agcctgaaca	agtccttctc	agagattctt
61381	tttttgcttg	catctagata	gacatgagaa	agctccaagg	gctaactcgag	gagaggacct
61441	ctccccagct	tacttagaag	gtctgaagcc	aagcataaag	gctaggggaa	aaaaagagac
61501	cagtagctaa	aacacagggt	ccgagtcaga	acttctgagc	catttaatta	aatgactttc
61561	attagttact	gccaaaggga	atgtaaatgg	gtgcataggc	tgtatgacct	taatcaggat
61621	agaacagcag	agggattcca	agatcatata	acgctatata	gccctcactg	gccagggaac
61681	gcctgcagcc	ccaccctgag	ttgataccca	ctcaggatgc	ctggctgggt	acagcagtc
61741	tctgactaga	cggtagtaat	tagaatgtct	ctttcactct	gatgccacac	ttcaagcggc
61801	taactgaact	gcttagcaga	ccggccaccg	gcactctccag	agcctgggtt	ctactggggc
61861	atctgagagt	cccagaatgt	ctgacagtca	ctgagtgtca	aagatgttat	taaaagacaa
61921	gaaggaaatg	gtaccaaagg	cagatcctgg	gacaaaggta	tctcaaaatt	acgcaacgct
61981	tttctccagt	cagcacctga	cagctcccat	attcccacac	cttggccagg	acgcttacca

FIGURE 6X

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62041 tcagctgcmc tgaaatactc ggggttcaca gaagcataca gcactccatt gcccacactg
62101 ctgttatttc tgtcaaaaaa aaaaagatga aaaccaggct aacaaatccc atctctatac
62161 atttctgtaa ataccttttc ttttcctttt tttctttctc acgagttatc ttgagcaagg
62221 gacgcaaacc atgatcactg ctgacgggac ccttgccctgc actcctgatc caggccccgg
62281 tatctgagga caaatctttc cacttttgcc ctggccctcag attagagctt ctaaagaaac
62341 atttgtttct ttgttctact ggaaataaca agggccactc catgggaagc taaactggca
62401 tgcttgagga agctcttaca aggcagcaat ctgtgtgcta gaacagccag aaagcagacg
62461 acgggtacag agaaggaagc aaccctctc ctgttgctgt tagtcattag gaaatgtcct
62521 tttttcccct ctgaagaatg tctgactagg aactctggct gtccagctct catggtatct
62581 tccccacag acgagctatg ttcaagttca aatcatcaag ccaatgcgcc acaagtactg
62641 tcttcgctg gcccaggcac tcacctctt ctatggaaga catacagcat gataaccagc
62701 ccccaacga tcagcaggat ggcaaccggc agagcaatga tcagatgcat caagttctca
62761 tacgtcgctg cagagacaag gaagacgtca cgcacagggt gaataactgg
62821 ctcaattcat ttctgtgtat ggttggaagg atgataaaac cgcctctgga atagccttta
62881 ctccctcatc tcacaagagg agtctctcag gagtcttcta gtgctgggac aagaccagca
62941 gacaaactga attgtttgga gaaaggtaaa taaatacaga ctgaagcaca cactccttta
63001 aagcactgca tattctgaat acagcaagta attctgaagg caagcccttc ctgtgtgtag
63061 ttttgtggaa gtttagctga aggaaaatga gcagacactc acacacttac tagttgctca
63121 cgctattctt atcttttaag aaagctccac agacagcttg ctgcgactc ccgtccccc
63181 aaagcactgg atgacactcc ctgccaatgt tgctctgagt gttctacaaa tatgtaaaac
63241 caattcaagt ctgaacttgc taccagtacc tgggtggtaa gtaccacagg atggcctcca
63301 ggggttcagg tctacacctc tgaaaatcct gagaattctg ccagattcaa gaactcagtc
63361 tgtggacagg tggattaaca tggatgtacg ctgggcatag ggggaagaag agatggggga
63421 gcgagggttg cttcccctag ggaaacggct tcccgtgcag aggaatgtct tgcagagtgt
63481 attgaatgat gaaggggttt ggttcagct aagtggtttc cgccccattc ttcagattga
63541 gaggagtcag tggtcagcag ttaagcctat gaactgcagc agtgaccagg atattagat
63601 gttcctcagt atgtaacact ggcacctga tctggggaca accaacagct gtctaagtgc
63661 actgaaggcc tgagcactgg gaggaaattc ttgccgatt ctgtaaacct agctgactct
63721 ctgtagtgtc gtggacacta gagaagaacc tgctactagc acttttctga agcagtgage
63781 ttctaccac agataactag ctctcaggcc tcgccagaga agcctctttc tgcagcagat
63841 ggaaaggatt agagaaaacc atgactggctc aaaatgcagg gaaccactga ccatggggta
63901 cccatgccc actgatgata gaccacacac acaaccccca caacaaatgc tcatggaaca
63961 ctgcaaaaata agtgcggtgt acgattctaa gatccagaag cccagggtgt ctgctgaggg
64021 atgccacctt ttatgtaaga caccaccgc atgctgtaac cccaacaacg cggttacctt
64081 aacttgcgta atgacaatac cagttcacat gctttgaagt gtgggggaatc tctgaagccc
64141 cacccttaga tgagaagtta ccagcagtta atggctgctg agagagaagg aggatcagtc
64201 tttatcaggc ataagcttgc tgatagggtta gccaatccca cgtggtcatc cctaaacaca
64261 tacatgtacc agtaacacta aatgagcttg gcagagcatg tgtgtatatg tatgtagggtg
64321 tatatgcata tatgtatata gacatatatg tatcaatgtg cgcacaagtt gcttagcaac
64381 aataattaa gtagtcatgg aactgagaga ggtgggcatg gaagaagctg ggagagggag

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**FIGURE 6Z**

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64441 gagccagatg gtgtaaatac agtactcatg tcagaagttc taaaaggcta aaactaaaac
64501 aatgaagaag aagcatcagt gaactcttcc aaggccagac tgaaaacgga ttcattgtact
64561 ggggaagatga gtgtgtctga ggacacactg ggggcctctg cacactgcca ggtctagagg
64621 agttaaggga acgtaccagt ctctgtgtgc atgctatgca tcgctccagt cagacctcag
64681 gaagaaatcc tttccataa gcaagatcag agaggcgctc taactttgcc aggtttgcac
64741 ggataactga caagttccaa agtcagagcc tggctttcct gcagccctgg ctcagaacag
64801 ccgcaaccca gtaactggga ggctggattc ccgtcatgta ccagaaagaa tcagtaagac
64861 tccagttaat atgggaaaac aaacaaacaa aaatgagtat gcggagaaga agaagcgaag
64921 ggctgtgagc tttcatctga gagcccaacg gaatgcagat cagggaatga aacggaccga
64981 agtgcctcca tgaagcact ttagatttca ggcttataag gagtctatag caactattgg
65041 acacccaagt tgacatgtct acacaataag gatggcgttg tgggtaaaaa cacttgctat
65101 gttaccctgg caaccagaat tcaatccctg gaacctgaga atcaactctt caatgttgtc
65161 ctctgacctc tgcacatgtg cacaccaagt acacaccaac agtatagaga tgtctccttg
65221 gaaaggagct ggggactcag tggagacatg ttcctggacc gcgagccact caccaatggg
65281 tgggtctacct ctaaaactcta ttcttaattc tgaataacta caaaagccaa aattaagtct
65341 ttttcaaaat cgatgggatt cagcaccttc cagtttctaa aagtactccc acgtgcgcct
65401 ccctgccaga gagaagctcc gagctttcct tttcccttag gagaattcgt ggtttttgtg
65461 tcctgattct acgggtcagg ttgttctgtg ttctttttga gtttcacatt tcaacaggga
65521 cacagaggaa ctggaaacaca tccagaagga caaaactgac agaaaattgt ctatgcaact
65581 ggctttcaag aaagggccca aagacctgag aatatttaat cgggagggaa gaagtctgaa
65641 gaggagttta atagaattca cgcaccaaga tttccttaaa aacagcaggt gatgccgagc
65701 tttcaatgtc cccctctgag gattagacct aagaaaactg tgctaaactg cgtcttgtcg
65761 gacaccggga aaattttcca gaagccaaga gcgctagcac gcagcttcaa tccccctgtg
65821 ggatgtgcc aactccactg gagaaacccc attagaggac ctcttaagag tccccagtgg
65881 cattgcagtc ttagctttac aaaggcagct acaaacatgc cctctcctaa gaaaagccag
65941 actcacttag cttcagaagt caagactgct ccttcagaga acaccaccca atttccagaa
66001 ctccagtgtt ggcttagtag cagcagtgct tacagataag cggaaatgta cccaaggcca
66061 gagatgctca gggcttcgtt gccggcctgt gacgttattg ggaagtagtg gcaggtaacc
66121 ttaggagctg gggtcttagag gaagtcaggc cactggaagc aggtgtcctg tgagagaact
66181 gtgaaacccg ggccctttct gccttttgga ggtaaccagc ttggttccat catgtgtctc
66241 ctgcttctga cattttgtct cagaacagcc caaaagtaat agaatacaac gacagagcac
66301 gacaaccccc gaaactgtgg gggccacccc tctaatacat tctgggtttt gccacatcgg
66361 agagctacag taacatcaca atggagagtt agcacataag ctaactgatg acgctaggct
66421 acccagaaaa aaatgagaaa attcagagtc tacctgacag aactctcagt ctcacatct
66481 ctcaatctag acacagtagc agcagataca gggaatccta gcttctctgt tacggttcta
66541 tttacttctg tctttgtgca gtcacgatga ggattttcga atgtcttgcg tatctttgaa
66601 tatctggaac tggctagggt ggctatcgaa gtgtgaactg acataaagtt atacatgtat
66661 acatattttac cacatacaac atatcttaaa gcatgtgtac attaacccaa tcagcatcag
66721 cattaagtcg cattgttacc atttctgtgg tggtaacact ttcttagcaa tattcaataa
66781 tgctttatta accatagcta gtgtgttata aagctcactc ttctatctac ctaaaattgt

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**FIGURE 6AA**

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66841 gtacctttttg agcaacaccc cctaagttat gttcccttgg taacctgcaa gactctgagt
66901 tcaccctttt agattttattt catatatatc tgagatcacg tgggtgttcc ctttctgcac
66961 cttctatttaa cagtattcca ttacatatat ggaccacatt tttaccacagg cacctgctgg
67021 aggatacttc attgtttggc tactgtgact agtgggcaa aaaaacaagg ggggtgtaga
67081 tttcaacaca actaacttcc atttcttttg gactgggatt gctggatctg ttgagacctt
67141 gtctgaatca agaatccaga agagaccacg aagaacataa gacattagga aacaacagtt
67201 cccacacccc tagattctag cctcaaagct gagctgagat tttggggggg ggggagtgca
67261 aaaggaattc acatttgatc ctgtatttgt ttggatatta catgaacacg aaataatcta
67321 aaaaaatttg gcttctcata agacacgtaa aaattcacta tgtattattt caccaaaaag
67381 actcaatttt tttttttttt cgggtcaaaca agcatgcagc ccttgcattht aacatttcac
67441 aacatttact tttaaatctg aatcctaaca gctcactcag tggtttctgt gaactgtgaa
67501 acattatcca ctagggtggg tctgtgcaaa ataacgcaca gagtatcttt caatgcattc
67561 tgggtgatgg tgaagagcac agaggagggg aagactctga ctgggatgtt gtcctgcaga
67621 ttcctgtccc ggagcagtga caccagacga tccctgggga gacgctgagc gctgggtcac
67681 cctcaccgac caggcaggag acctgatact caactcaatg ctttgcaaaa tgcctccaca
67741 cctgagccac gatgagaaca agatatcttc taggtgttac gatactcttc tgttactcac
67801 aagagaaggc tccaaggtc agcaccttc cagctctggg atgtgcgtgc gactgcacgt
67861 gcgtgcgagt gttgggggtg ggggaagggt atgggtggc agatgtgtgt ccactgtgag
67921 taaataccaa gtgtcttctt ttctggcgtg acacctcctg tttctagata cggcttctcg
67981 ctgaaagcaa aggtcaccaa tggaccattc tggctagcta gggatctgca aaactttgac
68041 tgtcgatctc ctgagcaccg aggaagcaca ctaccgcccc tggtttccgt caaggacttg
68101 aacttagatc tttaaagcagg cactttccct agtaagccac ctctcaacc cagccagctc
68161 tgttctaaca gaaaaccaga gagcccaga agctcagggc ttctgagttc tggccagacc
68221 agctttgaaa tttaccgtgc gtctccctca ataagactta cttttggcgg ggacatagaa
68281 gaacacagga tctgtccatg acccattccc agagagggag gtagcctgaa tccgggctgt
68341 atagttccct gggtttagac ggttgagttt ggcccctccg tacttctgtt actcctgtct
68401 ggacacacat tcccgtgat cctatggaaa tataaggcgt taatttccta caagcatggg
68461 tgagatctga catctgtcaa ctcaagtcac catgctgtga ctccagctgc ccaacctctc
68521 cttacattgt ccagagtatc aacataaagg aagcaaggat accggaaaag tggttttcag
68581 gttggcacat ggaaaatggt aatcaaatat gttggttaatt aaatcaaata tgttggtaac
68641 tccagaggaa taaaagatca tcaagacgtg tctagtctgc ggctggaggc ctactacag
68701 tttcattgtt tgtatgaagt ccagccagct ccatgcaccc aagttactac tcaataaaga
68761 tggcggttgct aggaagacct ttatccttcc cgactgccc tctttctccc ctgtctgctt
68821 agcagtcagc agacaaccag tatgcatatg cagtgctct cagcgctgaa acacatgcag
68881 ctgcaggcca tggatccct cttacctgca cttgcgaccc gtatttaatt tcatacatta
68941 ggatcaatcc gttggggttc tggggttctg gccactttaa aaagatggag ttttcgggtc
69001 ttggctccca ggtcaccgga ccagggatat catctgtctc ttctgcataa ttaatgtaa
69061 caagcagtc aattgggttt aggtccccag aaagaatgat aaacgggtgt ctaacttgag
69121 aacaactgtt ccccaatcc ttgtatatac aggactctgg acaggggacc ttgtaggagt
69181 tctttctctga gatggctgct ggcacagcgc ctccatcccc tctgactgaa aaaacctgtg

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FIGURE 6BB

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69241 gccaagtaca agtgatcacg cctgaaaaac ctatgtaaca ttctccagggt ccatttttcc
69301 acctaaaaag ttaaaaaaaaa aaaaaaagaa cccttcaaac agagcggccc tggggaaggg
69361 cagtgaagcga cagcgtgctg agcctccagc tgtggcactg acacattcac agcccacacc
69421 ctacacaggg agggaggaag ggccagttcc gaggctggcc tctgaggcag ctgttccggc
69481 cactgtctct tccagccacc gctggcctca cttctggtgg tgaaccacag ctgttggttg
69541 acagctgatg acagccgaga gaggcctggg gagataagct gttctctgtc tcttctagga
69601 ttgggaaact gaggcacggg tggctgaggg ctacacggga gtgccaaagc cgtctcaga
69661 agctcttact gcccagttc ccagcatgct ttgttctccc cactgactga cacctcctcc
69721 acgaatgaga agtggcaaat ggctggcagg gtgacaggca gtatctaact gtaggaggag
69781 gcccacaggc tgatctagct gaccacgagg acaacgcttc ctctgcatca agctttgaga
69841 cctggagggc ccctcacagg tctgtggtgt gctaaggcct ttgtgctctc agtctgtagc
69901 ctctggcact gagagaagac aggactttag gagattgggc ttcaatgaaa gaagtctgga
69961 aatacgatgt gttgcttcat tgcaagcccc aaagcagtga gaggcaagtg cctgtggtct
70021 aaaactcctg aaacactgag accaaaataa acctttcctt ctggtgaagc aactgccttg
70081 ggtattttgt aatagcaaca gaaagctaac tcattcagct gtgcacagaa gggcacaggg
70141 gtgggtgtga gcatgtgcat cgtgaaccaa gccaaggagt gagagccctg aaaggggctt
70201 gtaaagagtg tctatggtta agtctggatg ggagctggca ctaggaatac attctctgtt
70261 ccttaggcac ctgacggacg acgttgtgta ccaacaacca cacattcgta ggcctgaatc
70321 taagggctgt cagcctcccc cgccttggct gtaagtggc ggcggggcta cctgccgtac
70381 ctgctggcat ggttctcgca aagacgaagt tggaggcgct gcagccagc ttctcagcct
70441 cgtggttgca gctgtggata tcgatgcggt acagagtgaaggccggagg ttggagatga
70501 cagtcctctc cttgttatcc actctgctct caaagaaagg gtactctgtc tcgaactcct
70561 cggggtctgt gatattgtag gtgtcagcta ccgtggtgtt cctgcttcgg ctggacatgg
70621 tcgtgttggc cacttgcatg acgtctctcc gcctcctttc gggcctgcaa ggaggagaaa
70681 gaaggtcagc tgctaagttc tttagttttc tttgtctttt ccatggctag ggtagaagta
70741 ataggaaagt cctagccttg aactaaaaga aactacttag gctccttgga taagaaccaa
70801 caaataacca ggattttcgc cttcacaaac catcctgtac tctcttgaga catcctcaga
70861 gaaacatgtg cacacatggt tctaggaaac agtgtgccag ccatttttag ccagacagtg
70921 ctctgtttta ccagacagtg ctacttgggtc aggcctgata actgagcatt caacacgaca
70981 aaccatcagc ctcataagac tgggtgggaa aggtgaggcc taagacacac aaggtagaag
71041 agacccaaag tccaacagta gtggcttctt tgatcttctc tgaaatgaag atgccctagt
71101 ttaagcagct agcaagtacc taaatcccag cgcttttctt gaggaacagg gtctcctatt
71161 gatgaatgcc ccagtcctc agtacacagc atggtcttgg aggttcacat aacctggctt
71221 tgcctcctc ttggcagtga gcttgtctgt gataggagcg gacctctgt tactactga
71281 cttgtgttag ctttaagaaac tacagaaaag caacaggaac agagtctggg gctcctctc
71341 ttccagaaaa aacttctaac attcataaaa actgaaaaaa aaaataaata aaaatatgac
71401 atcagataag cagccctatg ggctggaagc aaccctcagg ttgtctgcag gtgaacagtg
71461 ggcaagctgg gtattgaggc tgttgctggc attgcttgtg acaggacaaa ggatgagagg
71521 aacagggtgg actgcactgc gtctggtaag aacatgacag agtaagacaa aagggagcct
71581 agagtacggg gctcaggcgc ccttgggaag catgcccaag gcctatggat gctccttagg

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**FIGURE 6CC**



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71641 ccaacatctg ggagagtaca gtagggagtt gggggaaagg gccgcatgct ccctgggtctt
71701 cagcagatgg atctgtctacc aaaaccatag ttctttgtcg ggtactgaca tgccagtttc
71761 cattgaaagt atatcaactg ccataccagg gcccatctca aaagttagga atggggattt
71821 gttatcataa tgctggggaa agagatagga aatgagggtta ctattctacc atgctcacac
71881 ccagcaaacc ataaaccgac caatcaacaa accatggaag gaaagataaa ggaaactact
71941 ttttcaggta tgtgtgtgcg tgcattgcatg tgtgctgtcg tgtgtgtgtg tgtgtgtgtg
72001 tgtgtgtgtg tgtgtgtggc ggctaggcag atgttcaaaa cattattatt aaatttctctg
72061 cctccctttc aaaccagagc aacacaaacg tgtgccttca tgtaagaagt tgcttgtgtt
72121 tgattttattg caaaatgata ctgggtccact tcttgccctg acccaccccc aacaaactgg
72181 gctatagcac caagcagact cagtggcctc cttacttata aacactgcac tcttgcatat
72241 tattcaacag ttactgtgga cacagagtca ggaccatgaa gggaggcaat ataggcatca
72301 gaaggctagg gatgattcaa acagagtggc ccagggggtg gcaaacagca gctatcagc
72361 tttccttact ccataaagta tcctgatgct actggaaaaa cttgtactgt ttaacatctg
72421 agaattgtttt agtgacagaa acatttttga agcgtcttca aaaatgaaga tggcgcccaa
72481 tgaaagccat ttactgatac caagtttagg aagtaacttt ataaatagta gcctccactc
72541 tactataaac tcacaggcaa agtcagacaa tgcagaaaaga ctaaactctga tatatttgcc
72601 ttcagccccc agataaacgt gcacctagaa tgacatgaag gtaggaatag gttttaggta
72661 aactcgggtg tatgatgaca gagttgctcc tgtcatctag ggtgctcctt tatgggacct
72721 tgcgagacct cgtatagatg tcagatcctt gcctcggtag gaggtaaaaa acaacccccc
72781 aaaccctaatt ccagagtggt ggtgacctt atctgcatgc tgggtctgtt ttaggacact
72841 gaggtgagga cacttacacg aaggaatgtg accgagagaa aattcgtttc aaaccacag
72901 tacaagccct gcacggtccc atctgggtca accacagcct tgccgccccaa tcacttagcc
72961 tagcgttaca cagctgatga taacagcagt cacaaagtga tgtcatctga gtataactaa
73021 acaccaaggg ctttctgcta tgggtcgtct acccttggtt ctcattgctgt attggttagat
73081 gtttggtcac tagtggggca gctgcaggag gaacctttag ggaatggctc tgttaggggg
73141 agatcctgat gtagcaaaac agctaagtgc tcaacgtctg ttcagcttcc tgtctgccct
73201 gaaatcgctg ctgtgccata agtacttttg ccatgcgaca cacccaaaga tgccttcac
73261 aacaaaagcc acactggctc cttgttcttc taactttaaa actgttgagc tatgcacacc
73321 actaagcatc acgcaatttg ttagcaacaa tgaaagaacg acctaaacct ctggccatgc
73381 ctacaggagt cctggatttg actgacaccc agtatagggg tgggtatggg aggacctctg
73441 cctggcctct tggggacgct ccatacctgg ccactctcat ggctactctt actgagtgtt
73501 ggttcagggtg gaatgctcca catagataac ccaatgaagg gacggagggt tgggtgttga
73561 gaatgtaggt ctgagaccca agactcaaac agacagtaag ttagtgagga tagaggtcac
73621 tgcattccagt ttttaaagca ctttttgatt tgtttcctgt cttcagggtc ttaaattcaa
73681 agaaacagac atgacacaga ggggaacatg ggtaaaagcc aaaacagcag cgctcctgt
73741 cagctgactg caatagcagc ccagcagcct gccaaccaac aggagctgct ccgctggggg
73801 cagatgggag catgcacagc ctaaggcatc aaatgtagcc tttccaaagg gcacactcac
73861 ctgggcacaa agatggaatt gtgaaggaaa ttctcaaaga ctttacggta ctcagcctcc
73921 tccttctcag cctgcttctc agcttcagtt ttagggcaag cgagcatggt ccctttatca
73981 ccaccacaca cttctgtctt gggattttcc gtcacctcct ccacgtcgat ggtaccatcg

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**FIGURE 6DD**

74041	gcgtactttc	tgatgggtat	tttgtctgct	tggggaagac	cagagatggg	aatgaaagcc
74101	atgcaggaag	tgccctgttag	cattgtctggt	ggaggggagg	gggtgctggtg	tgactgtctg
74161	agaagcaagc	cctgcaacgt	gacaggtgtg	accctggggc	tcaggttctc	tcagacaaca
74221	gacaaggcca	gtggcactgc	ctgectgtctg	cctgccagcc	cccagctcac	ctttggagca
74281	gtagttgtgc	cggtaacaggt	aaccatcctg	gggctgccgc	tgccacctca	caatgtagta
74341	actcaagtta	ccattgggca	gagttggagg	attccacttc	acaatcagct	gagaggaaga
74401	gtttgatgct	gagaggacat	ctaggggaat	ggaagggact	ggaaagaaga	acaaagaaca
74461	tttcagagaa	tagaccggaa	tccgaggttg	aggttatcag	gggctcgatg	caaaccaaca
74521	ggaagctgca	ggcttgacct	gggcacagag	atagcaacgg	accaaccaga	gcatgaggtg
74581	aaccagagct	ttggaaagat	taccaactgg	gaggccagcc	ctctctcaga	gcacttgctc
74641	ttagataatc	tatgtgcaaa	cacacatggc	tcactgacct	gggactgaag	gggctacgag
74701	ggcatagtcg	gggttaaagg	ggactctaaa	aaaaaaccta	gagttgattc	agtttagaca
74761	actgtcatte	tccggtgtgt	attaggaat	ggcaaattgg	acggcttagt	acttcacctg
74821	tgattgcaag	ttttaatctc	tgataaaaac	ttgataaaca	tgacagggag	ccaaaatgaa
74881	gagtgaggag	gggggatgga	cagtgtgtgg	gggtggttatg	tgccctgggtg	aaaggactgt
74941	gaaacaagga	gcagggactc	acagatcttg	taagcaagtc	atgattcagg	aaagccagta
75001	cgcctgagcc	ctgattctat	gcaaagtcct	gttacaagca	aatgagttta	acaaaacgac
75061	ggaggcttac	atactactga	tgcccaggct	caaaagtaga	actaacttac	gtaaaaagga
75121	aaacatccca	ggaccactgc	tgtgtctcaa	ccatagcaaa	agagatacca	cagccgaagc
75181	gcaccccatc	cccaacacac	acacatgcac	atggcaaaaga	atgaggccca	ctggtttttg
75241	cagttttcaa	agtgcagag	acagaaccgt	ggttatgaca	cttaagaata	aggtccaacc
75301	aagctgtttt	tgaatctgaa	aggtgaaaac	aagcttgtac	cggtcagtct	tatgacaact
75361	tggcacaacc	tatctgacag	aaaaaaacct	caactgagag	gatggctcag	tatgatcagg
75421	ctgtaaggca	ggcctgcagg	gcactcttct	aactaatggt	tgggtggagga	aatgccccagc
75481	tcattgtggg	gaggaggcct	ctgggctggt	ggctcctggg	tctctaagaa	agcaggctga
75541	gcaagccact	gggagcaagc	cagtgtcttc	ccaaagtcc	tgtctctgct	ggagtctcta
75601	ccctggcttc	cttaacggca	gactgtgatc	ctgatgtgga	agtcaaatcc	tttccttgcc
75661	aggtcatata	ccaccacacc	aacaggaagc	gaatggacag	agggctgtta	ggatgtatgc
75721	ggtgctcaag	gctctgagaa	ccactgaggg	acaacacgtt	ggaagaccaa	gactgatgca
75781	gagaagacaa	gcacttgatg	cctggtcccg	tgagcgtttt	caataagtat	ttccaaaaca
75841	gtttcttact	aggtatttca	atgacaagtt	tcccagatga	agcagaggga	catgatggac
75901	taagtacgtc	actatcgggtc	ccaagcactt	ttgaggtcag	ggaccaaagt	cagtttttaa
75961	tatttaggaa	gaagaatagg	atttcttaag	aatctgctat	aatgataaga	aattcctgct
76021	tagttttttt	tttttctctc	tcagatctgc	tgcaatgatt	cactgggagt	cattactccc
76081	aaactttaag	atgagaaatg	tattcagttg	ctttgctctt	ggaacgggtga	atatgtttca
76141	ttgtgttgta	agccactcaa	gtcgatggaa	ttttttgttg	taagaggtca	gtcattatct
76201	ttacagtga	gcatactttt	ctacctctct	cgtcttttga	tacaaactca	cacctttgct
76261	tttccccact	tctaggttct	ggagctgggg	aactagtacg	taaacacatg	aagaagatga
76321	gaagggatta	gtcaataatc	cgatatcata	gtactctaag	cctgcgttcg	cctggtgaga
76381	aagctggtgg	ctacggaata	aaggtggaaa	gccagcaagc	cactagaggc	aaggggtgca

FIGURE 6EE

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76441 cccggtcattg tccgtctcagt ccctggaagt ctgcactgag agagaggaga ccagccacaa
76501 gtggctacat cctgggcatt cagagaaacc atcctactgc tctggaggac accgattcaa
76561 ttgcgtagag cagagatggt gacattttaag atggtaccaaa gtctaggaaa tggtcagga
76621 gaacttaagg tggtggcagt gagaatgta atacagtgtt aagcagcaac aacaagcatc
76681 tcattgctag ccctccagcc atactgtgcc tatgtaaaata aagcaagctt ataaaaattc
76741 agggaacagg ggttggagggt tggtccctccg gtgcgtggat acctgaagca ttggtgcgaa
76801 tgtacaagat ttcaacttttg gccccacgga tatggtcgtt ttccaccatg gtgaggggtca
76861 cagccttgac atagacagca tactgggtcc agggcttcag cccatgcagt aaaatgccag
76921 gctcgccctc cttgttcgga ggcaggtcta catccaccat gttccagctg ttggagccac
76981 aggcacccctg cccgtcatat tccgtaacgt ttttaaatgg tctgaaagac agtcaacaca
77041 ggccagagaa cgttgaagggt ctctggcacc aaaactcccc agaactttcc ccaggggctg
77101 aacgtgtcac actttctatt tctattggga actccaaaata aaactcatca tcaattagat
77161 ttctatacaa aaataaaatc aagcatctgg actcggggagc tcgacagcta tgaaccgcag
77221 aactgacaag cagccttaga gacagcaagt ccctcattca cagggactga aaatgctgcg
77281 tctaagacat gcggatgtct attgtcttct taagtgcagag ttaaaaaacaa caacaacaac
77341 atcaacaaaa acccaactaa tgaaaaaaaa aaaaaacaaaa aacaagcaga gctgtttaat
77401 gcaaacataa aactaataaa acacaacttt tggacaaaac taactttcct atccccctag
77461 aactctaaaa tgtaattcga taatagccat ttttatttat ttttattttt acttttttgg
77521 tttttcgaga caaggtttct ctgtgaagcc ctggctgtcc tgggaactcac tctgttagac
77581 aggtgcacct cgaactgcct cccaagtgcg gggatcaaaag atgtgcacca ccactgcctg
77641 gctcataata gctatttttt ttaacaatt tttttagtag atattttctt catttacatt
77701 tcaaagtcta tccgtgaaat ctccataacc ctccccccgc cctgtccccc aaccaccca
77761 ctcccacttc ctagccctgg cattcccctg tactggggca tataatcttc acaagaccaa
77821 gggcctctcc tcccaacgat ggccgactag gccatccttt gctacatatg cagctagaaa
77881 cagagctca ggggggtattg gttagttcat attgctgttc ctccatagag gttgcagacc
77941 ccttcagctc cttggatact ttctctagct cctccattgg gggccctgtg ttccatcaa
78001 tagatgaatg tgagcattca cttctgtatt tgccaggcac tggcatagcc tcacaagaga
78061 cagctatata tgggtcatgt cagcaaaatc ttgctgggtg atgcaatagt gtctgcgttt
78121 ggtggctgag ataatagcta ttttcgatgc ttaactatct cataatattc caacactttg
78181 tttcctgatt gtctcagaga gtggcattgg tgataccacc agttagcatc gccagtgcac
78241 tggcagcact ttcaaaggga agggaggggt ctgcacagat gcatggtagg cgggggtgtc
78301 actttgacga gatgcaagggt ctgctagcta ctggcttctg aaattatgct gacatgactt
78361 gtgttcgatc acgatgggag aggggtggcc cccatttaca caaacactga gtgattttga
78421 gctttctatt ttccctgggc tataacagtt cccaggacc taggtcaagt ggcagcgaag
78481 ataccaggca ctgccaccag cacctttgct tctggaaaga tcagtgcctg ggaaaacgga
78541 tgaccacaca gactggggaa accacctggc cacaggaggc tgagtaggaa aatgggacag
78601 ctcaggaagc tgtgatgtgg agtaagcagg atggtcctat caggaactgc tgacacctag
78661 gttcgtccct cactattctt taatgctaga gggctcatgg cccagagcaa agtcttggca
78721 aggccatgca tgcatacagt gactggaaga caatgggtca gttcagggtg gccttgggtg
78781 gaacagagca ccccatgggg tattttgggg gacagaggct aagacaatat ttaaccaagt

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**FIGURE 6FF**

78841	ccacataatg	gcttatgaca	gtttggagge	attcagttct	cttaaaatc	atcccccttc
78901	cccttggggg	gaacttactc	aaacaccata	taaacaatga	aagggctgag	gcgggacact
78961	ctcctgacta	gctgctgtct	caggttggga	cagtttaata	tgacaactag	agaggtcaca
79021	tgaggatgag	gtgacggtcg	cctgacttga	ttctttatag	gtacaccaa	gactctctat
79081	tcagccaagt	cacactgcca	cctggccgct	cccaccctca	agcttgacat	cagagtgaga
79141	ggcccaaaact	cacgcctcct	tgtagtaaac	tgtgaagctg	atgagatccc	ggtagtccgg
79201	cggccgggtac	cggtgccacg	ttatgatgat	tcggttcttc	caggtcgtgg	tggaggtgaa
79261	acggagaaca	tcactttcac	ctggggcaca	gaggcacatc	catgagtgac	agaaacccat
79321	ccgtctctgt	gatgtcactc	tgagagaaaa	ccctgactgt	gcttccaaag	gcaaactctat
79381	ggctggcgca	ctcatgacct	gtcaggtcag	gctggctgcc	cctaaggag	aagccctttg
79441	aaatgctccg	atcacaggct	tctgctatgt	tcctgatggg	gaacagggtc	gggggctctg
79501	cagaaagggtg	aggggtgctgg	ctgtgtacac	acttaccacc	tctgcctaac	tactcttctc
79561	aagatgcctc	ctggatccgt	agagtatcag	ataaatctgg	atactcaaaa	gacaaggcta
79621	gccctcccc	cacatgtatg	cacacgtctg	actagctggt	ggtcacacag	ctcctgatcc
79681	cccactaatg	ctatataatg	acggaggggtc	aaatagagct	ttagtatttc	tgtttgtttg
79741	tttttgtttc	cttaaaacag	ggtttttagat	gtagcccaag	ctggcttcaa	actcacaatc
79801	ctcctgcctc	agcctgttaa	gtggtgagat	tataggagtg	taccatcatg	cctagctcca
79861	tacagtgcta	gaggagagac	tgacatcagc	gctctgggacc	acatttggag	aggggctggg
79921	ttaacagggtt	gaactctagg	ctatgagatc	ttagggtgaa	aactctcatc	accaggatgg
79981	aattattact	ttgtccaaca	tgtgaaaagc	attccgattc	aaagacatgg	gctcactttg
80041	ttctagaagg	agcagggcag	agaaaggagg	ccaagtgtga	ggacaaggac	actggacgct
80101	cacggaagta	ttatagtggg	gcactctacc	tgatccttct	atggcacagg	agagaaaggc
80161	agagctgacc	tggagtggac	tggctcttcg	gtaaatattg	tttgctcata	ttgaaaagg
80221	atttaactgt	gcaagctcta	agaacctgct	tggatgttta	atagactcaa	atggaccctt
80281	agaaaaatat	atcagtatga	gtgtatcagg	caccgcacca	ctaatatgca	gaggccaggc
80341	actggctgca	gtggtttgac	agtccatggg	gaaacaaaaga	gcccgcccac	ggatgccaaa
80401	gactgttata	tggactgtgg	cagtcccagg	ggcttgagat	gctgtcactc	acaggaagct
80461	cgctctccgt	tgttcctggg	gtttatgtcc	cctttgctct	ggcgtccctt	ggttccgggtc
80521	acttctccca	tgcggtaaat	ttcggagaca	cacagcttgg	gattgaaagc	aaagtacatc
80581	tttccggacc	tgacggtcag	gttccgggtg	ttccagtccc	acagctgctg	caagttctgg
80641	ttgtctagga	catagaagga	gtagttcctg	gaagcacaga	aatgcgcatt	agcaacgcac
80701	tgagcccaca	gccccctcag	gcgacagaga	gcctctctgc	ggccagtgtg	gttccatacc
80761	aacaaggggt	ttgcttgctt	actgggggctt	tataacagca	gacagtggcg	gtagccactg
80821	gcaaaaagat	gtgccaaagga	caatgttttg	aaatcgactg	gacactaatt	aatttcatga
80881	cctctattac	caacacacaa	agcttctccc	accaaaggat	gttccttgat	tcattccctg
80941	ggaaaatgcc	tttggttatt	tctctcagag	ccaggtatgg	acaatgtgct	tgaatcagc
81001	ctacaggcga	acagacatgc	tccgtactc	aaccggaaca	gcttacatac	tagcagcaaa
81061	ggctgccatt	atccctagga	ataaatccta	cccattgcca	atcagcagtg	catgatggga
81121	tgggagacag	cctgggtctc	tgtacatttg	cctctcgctg	caagaagcct	tcatttcagt
81181	ccctgagtac	gtgggagagg	acagacatcc	agtgtctccc	tgggctctca	catcagggta

**FIGURE 6GG**

81241	gctagatgca	gcgtgtaaca	tgggtggcttt	ccacatttag	tatgtacaca	gcttgtttctc
81301	agtatccct	accgctagag	cttctgggtgc	agagggtccag	agtgcaccag	gaatctcgat
81361	gtctagcagg	taatgctgat	aaacaccagt	cctgggtcca	cccagaaact	accaggccgg
81421	ccacggcact	gtttccaagg	cctaacttcc	actagagggg	agatatgggc	atggccaaag
81481	ggaagatagc	tatcttaggg	ggccaagggg	agagcaagga	ttctacttgg	gtgtctgcat
81541	aagttttttt	ttttttttta	aacagttatt	tctaaatcca	cccacagacc	agacaaacat
81601	gtcccaaagt	cctgttctgc	cctaaaggct	gtgtccacct	aggcaccacc	tgctgagagt
81661	cctcaccac	attagaacta	ctgcctaggg	ggctctgcttt	caacatgacc	ttcacatact
81721	gagaaatgag	ttacagctgc	agggttgcca	agcctctccc	gacacttcct	ggagaactca
81781	ttagggagct	cagaggccag	gaccaggac	cggaagagcc	atgaattccc	cacaggacaa
81841	gccacaggca	gtttcctcgg	tgctatgaag	agcagcggtc	atgtgcgtag	gtgaagtctg
81901	aggtctcggt	ggttttaaga	ttccttatga	gagccagtga	gatggctcat	gcgtgcaaga
81961	gtacttacat	cacaagtctg	gtgatcagga	ccccgagaag	gaagaacagt	tactgtgtaa
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82081	agtcggagct	caagtgtgag	ctaagcagtt	gaatggaagc	cccaaccctc	cttgagcact
82141	tctgcgcagg	cttcagcgca	gggtctgcac	acgcacgggc	tcaatgagcc	gctagccttt
82201	ggtaaggagt	gttcccctac	catgcttggt	tattggagta	ggaaacaaag	accctgatca
82261	aaggaatcca	gatcgtagta	cctaagagtg	tatgtcctag	ggaggtcctt	ggatacctgt
82321	cagtcagaac	tgccacctac	gggacccacc	aatgttcact	cttattgata	tgggggtggt
82381	caggataggc	agacaactga	aggataggtg	taatggtgga	aagattgggt	cccattaggt
82441	gtcttgccct	accatgggcc	attctttaa	tgctgcctca	acgctaacct	caccggctctg
82501	gctgtcctcc	agtcttgaga	gtcccaggag	acaaaaatct	cctgttattg	aagacacctc
82561	caggccggat	acaagggcca	actaatcagg	tcaaaactccc	atctccatct	aggccaaggc
82621	ctcttagtaa	actaatttct	caagcaggaa	acagaattgt	actgaaaata	ccttccttct
82681	gagccacaca	ttcttctccc	cagggaggga	gcatgaatta	gaaaccagga	atttgacaaa
82741	tgaatggcag	gcacatagaa	actcagggtg	tttgactaat	cactttgaaa	agcaagatta
82801	tcttttcaca	gtaaacacaa	actttctctc	tttaaacaa	gcagagaagg	ctgggagcca
82861	gaataccaat	atcaataaaa	tccaggcatt	gtggagccta	cagaaggtaa	agaaaaataa
82921	aaaccttcac	caaaataata	atcaacctgc	tggggagggc	ccgtccacac	agtgcctgct
82981	tcccaacccc	cacccgaggc	ctgcctcctc	aacaccttct	gcaatagtga	gagttaagag
83041	atatccccag	gtggagattt	gtctacacac	cttcaagata	ctaattgtcct	tgaatggtca
83101	ttgttttctc	agggagatga	ctagttaagg	gaaccactca	ataaatgcga	cttcataaat
83161	cgtttctaa	ctcactgcct	ttttacatcc	acagaatatt	tttaaaaacc	aaactgttca
83221	ttttttttcc	tttggtctct	acacgctgta	tgatctcccg	gagttttatt	gagtgggtatt
83281	ttggtcttta	gttcgatcct	tccttctttc	ctaccttctc	ttctgcaccc	ccccacccc
83341	ctcaagacag	ggtttctctg	tgtagccctg	gctgtcctgg	aacttactct	gtagaccagg
83401	ctggcctaga	actcagaaat	ccacctgcct	ctgcctccca	agtgtctggga	ctaaagaaat
83461	gtgccaccac	tgcttggtag	cttgtagctt	tttcaacatt	agaaaaaaa	atccccctta
83521	ttggatgggt	ttcacctgcc	aatgcataga	cctactagga	tggttagtca	acaatttggg
83581	ggccctgtca	catgataagc	tcacagccaa	cacttagcta	tgatctgtgg	ctaccatttc

FIGURE 6HH

83641	taggcctccc	ttttaagtga	agactgcagg	ggaccgagtg	tagagtcttc	catgtaggaa
83701	ctgataacca	ggcccaagca	ccttctccac	tgettattgaa	gtggcacctg	aatgggtttac
83761	tcagcttctc	tagggctgct	ggttctcagc	tgcccatgga	gctatctttt	ctggctctctt
83821	cgggccccga	ggccaattga	gaagaactgg	atgctaaata	taaaaggacg	ttataagctt
83881	tgaatcacct	cacaaaggca	caggatgacc	tgtgctactc	tctgaactgt	caaaagtccc
83941	ccagaacaaa	gtcacagaaa	ataggtaagt	cctgcacctt	gatacaggca	gggctgagct
84001	caaggtctcc	agcctacaca	ggaccctctc	ttcaagctct	tactggcatc	ctggaagcac
84061	agacaaccaa	taactcatat	ccatTTTTgc	aaggagacac	tactactgcc	tgtgacagct
84121	gtctctagag	ggcatcagaa	gccagtacac	tgaagctgtc	accagtacag	tcatttataa
84181	cactacttag	cccatctgta	gaatattggt	tcacttcagg	tccacagtta	taccatctac
84241	aaaggctcag	ttagtatgga	aatatatacc	caggcaaaac	taaaccaagc	accacataga
84301	ttgacaaaat	aggccgtttg	ttcctgagtg	ctttttaaaa	acagctttgc	tgaggtagct
84361	tttaccttct	aaaattgttc	ccactataaa	tatacagctc	catgggcttc	aataaattta
84421	tacagatggc	caatcatctt	tcaatcatcc	agattcagaa	catttatatc	aaactgaagc
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84541	catgtaccat	tggctagtat	cttactgtgt	gttttgcgct	tatactgagg	aacccttaga
84601	ttatatctaa	cgcaccattt	tgagaaaata	ctatggaaaa	tgttgctaag	agcattcaca
84661	tgtgatattt	gcatacacat	gcttccatat	ctctaggaac	agcctagact	tgttaggcaa
84721	agtaactaat	tgtatgtatt	ttaaaagtcc	caagtatgtg	ctaaaatgtg	gttatgttag
84781	ggtctagttc	cagagatgca	gggcacatta	caaaaccctg	agtctgcaaa	gggtagagat
84841	gcctaaacag	actaagaatt	ctaactttat	actggccccc	ttccagtatt	tttgttctgt
84901	tcaagacaat	aatctttggc	agcacctaag	agcttgaact	tttcatttat	ttgattgctc
84961	ccaaacccaa	gttgtccaaa	gcagagcatt	ttttttttca	gataatggaa	atattttctc
85021	tcttattcaa	ggagaaccac	atatccctat	ccccagacaa	aacttgattt	tccttcttaa
85081	tcccccccat	gacccccaca	ctttgtctaga	gatcaggtag	caagcaccac	acactctagg
85141	ttaagtgtct	tatcactaca	ccacaccact	acttctgaga	aaaccctttc	ctttctgtgt
85201	ctgtccttga	gtacacagac	gtgcaggctt	ctggacacag	gagagagaca	ctgggcatcc
85261	tcctgttact	ctctacccca	ctgtcctgaa	acaggctgtc	tcacggagtc	tggctcagggt
85321	caggcaggtc	atctgactag	caagttcttg	ggatcagctc	gtctcagctc	accacctgga
85381	gtactcctg	ggtgcagcta	ggctcagtea	cgccgaggat	tcaaacacga	ggcctcatga
85441	ttgccaagca	agtacactta	gctagggagt	catctctcca	actcctatga	tcttatctga
85501	agttgggatt	ctacagctat	gccacactac	agagagagtg	atggctgaga	ccaaaggggtc
85561	ctgctgctac	ccaagtaccg	ttctgtggct	gtgcaccctg	atgtctgtct	tgtgtggatt
85621	ctgcttcacc	tgtcgtcggc	ctggaaaatca	gtgtacagaa	atgtggcctg	atgagcatgc
85681	atgacccagg	taagcaggcc	cagaaaagaa	acacaggaac	tacacgccag	gcaaaacact
85741	tgtgttccca	cgggggggcta	ccgagaaggc	caagatcaac	tgcagtgtct	tcctggatag
85801	ctaaggctga	aggatacctt	catgggggtg	gggggtgggg	tggggggaaa	tattcctctt
85861	tccatcaaga	cagaagtctt	cagaatcctc	ctgagccgca	cgggaagcatt	tatgccattt
85921	tcagtagcca	tacaaaaagc	tcaagaaata	gattccttca	acactgagtt	gaggcaagat
85981	tgcttaaaaa	taaaataaaa	tataaaataa	aataaaaact	cagaagtggc	ctgggactat

FIGURE 6II

86041	atacatttga	aggatcacag	ggatagcgaa	gtcattttcta	atcttttgcca	tgtgccaac
86101	atacacagaa	atactcagaa	agttactcga	gcttatgctg	gcaactcccc	cacccaagt
86161	tttctgtctg	acttgggggtg	aggtdaacct	ggdgaagtgc	cacagggctc	ccctttccct
86221	gtaactgtga	tgtatccaca	cattcttggga	aacactgggg	ggagggggag	gaggctatca
86281	gtataaacga	cagcaccctg	aaattaaatg	tcagataact	ctgctaatac	acccctctc
86341	aaaatctcca	gtgcgtccca	aggcttacct	aaatgataac	ctctacatct	gcatgcaaca
86401	gtgcctccta	taatcctagt	actgcctacc	tccccagga	gctgaacaca	agacaggccc
86461	aaatgtcatt	ctgtgctctc	tcctcttctg	tccctgtgct	ttctagtccc	ccaaaccctt
86521	ccaggccagc	tttgctcaga	agcctgtgtg	gccttctcca	ccagagtctt	ccttttggta
86581	cccagagcac	cttctgtcct	ctcctctggg	gctctctgaa	gcctgtgctt	tgcactacct
86641	gtgttcattc	gcttattaca	aatctttctc	tcctttatta	aataagttag	gaagaagtga
86701	accagctgag	ccctaatact	atacaacgag	agacaaaggt	gagttgttgc	tatgggtggc
86761	ccctcaaagc	tttggatttc	atcacagtta	ccagagaaag	ctactactaa	agagtctcaa
86821	atgtcctggc	cagagatata	cttgaagcaa	gaggctctca	acctgtgggt	ttagattcct
86881	ttgaggtcaa	atatcagaca	tccttcatat	catgcattta	cattacaatt	cataacagta
86941	gtaaaattac	agatatgacg	tagcaatgaa	tagatttatgg	ttgggggtca	ccactacatg
87001	aggaactgta	ttaaagggtg	gcagtactgg	aaggctgaga	aacactgttt	tttaacacaa
87061	gtctccaggc	ctcacctgcc	ctccactccc	ttctcaaata	ctaacagcag	ggctggcgct
87121	agcttttcag	ggaagcttcc	ccaataaccag	aatccttaac	aataacttggc	tgatatttat
87181	agtagccaga	agctggaaac	aacctagatg	tccctcaaca	gaggaatgga	tacagaaaat
87241	gtggtacatt	tacacaatgg	agtactactc	agctattaaa	aacaatgact	tcttgaaatt
87301	tgcaggcaaa	tggatggatc	tagaaaatat	catcctgagt	gaggtaactc	aagtcacaaa
87361	agaacagata	tggatatggac	tactgataaa	gtgggtacta	ggcagaaagc	atggaatacc
87421	cacaatacaa	ctcatggacc	acatgaagct	caagaggaag	accaaagagt	ggatgcttca
87481	tcctacttag	aaggggagaac	aatataatca	aggggaagtag	aggggtgggag	ggatttggga
87541	agaagaaaag	agggggaggg	gaaaagaggg	tgcagagtca	ggtattgaag	gagctagagg
87601	agatgtacag	agggtcagga	aattgaacag	aggggatggg	gaactggagg	tagcaaccac
87661	aaagtcccag	atgcgaggaa	agcaagagcc	tcccaggacc	ccatggagat	gacattagct
87721	gaaataaccc	acaaagggga	aggagaacct	gtcaagacca	tatccagagg	ttagactgcc
87781	ccccaccccc	gttgaaggat	ggggcaaccc	acccatcttc	aaagttttaa	ctcagaattg
87841	ctcctgtcta	aaggaaatac	agggacaaag	agtggagcag	agactgaagg	aaagtccatc
87901	cagagactgt	cctacctggg	gatccatctc	acacgcagac	accaaaccga	gacactatct
87961	attgctgatg	ccaagaagtg	cttgctgaca	ggagcctgat	acagctccct	cctgagaggg
88021	tctgccagat	cctgaccaat	acagatgaag	aggctggcag	ccaaatatca	gactaagcac
88081	agggacccca	atggagaagt	tagaggaaga	actgaaggag	ctgaaggggc	cttatctggc
88141	atcaatggga	ggggaggccc	ttggctctgt	aaaggcttga	tgccctagtg	tagaggaatg
88201	ctagggcagt	gaggtgggac	tgggtgggtg	ggggagcacc	cgcatagaag	cagggttaag
88261	tgggatggga	tagagggttt	gcagagggga	aaccaggaaa	aaggataaca	tttgaaatgt
88321	aaacaaataa	aatactcatt	taaaaaaaaa	aaagacttgg	ctggtacttc	atacctaagt
88381	tttgaataat	gaaaaaatag	gctataaata	ttcttggaaa	taaaaaccag	ccttcaatct

FIGURE 6JJ

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88441 tcagcaacat ctaagtgtat gatactttta gttaaggcat aatgataaga taatcatacc
88501 atgtaataat cctgataaga aataatcaaa gcctcctttt gacttttctat gcctatcgct
88561 tgctcagtg tggaaaaagg ggtgggggag cttatcctcc agtaactaac agatctgaca
88621 gctactaatc cgccaaggaa aacgtgcttc ccgatgtcag ggagtatagg gcacagatct
88681 actgggggga cataatgaaa cgagatggag ttacagttca ctttaaaatt taatacaagc
88741 aacaatgaat taagggtgac cacggcctca tgtacgggag gccccagaat gattgcgaca
88801 ctctgggcag ggtacctggc acatgcagaa ggattcgcaa ggagaaggag gtttttctga
88861 agcttctctg ctgcgaatgg gaagatggac ggggtgagca gctctgtttc tggctgtatg
88921 taccagggga agacccaggc cagagttggt gtgagaaaaa ctggagggtg taaagaaacc
88981 tcattccagac ataccagcct ggggacaagc cttctccgga tcttcccgtc actgtctttc
89041 taagggccct gattgcttag ttaatacacg tataaaactt caaagcatta acacagagct
89101 acaccagaga cgtagcaaat gtctgaaggg gccagcaagg gcacacaggc gagagtctgg
89161 aaagaagctg tgtgcacatg cagtaagcac cagctttact ctctgctgag aaaccacagg
89221 ctgctttaaa acccagcttg caaagcattt ctgtgcagaa ggcacaaccc ctatcaatac
89281 tccaaatcct gaaagctgat caatacacag acgctgtaag ctaatcaatg tacaagctct
89341 gcaagctgaa atatctctgt aataaaatga actgtccgta ctttgcaatt ctttctgctt
89401 ctctgtttga aaaggagatg gcttgggtgt caggtgtcga agtgcttgct gtacaagaga
89461 acccacgtaa catgtgcctg aaatctcagc acttagaaag tggacacagg gacatctctg
89521 aggcttgtca gccagttagt ctacaaactg gtgagctcca cgttcattga gagacatact
89581 caaaagataa gatagagaaa aaagacaccc tgtgtctcct tgaacctcca gaggggtgtg
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89761 tgaatcacaa tttccctggg agttaagcac cacaggcagg ctgctgtcac tcctgcagga
89821 aagggtccct gggaatacct tggactgcta gaactcagcg ccctagetta gactcgtgtg
89881 gtggtttgga tgagaaatgt caccatggg gtcacacatt tgaacgaacg gccccaggag
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90361 gtaacaaacc caaggatatt tgaaaagtac actaatcggg gctgggagct ggctcagccc
90421 ctaagggtaa gggcagctgc tgtcagggtc ctacaacgag tggagttgaa cccccaggag
90481 ccacttgaca aaaggagaga ctgactccca caagttgtat tctgacacac atacacacac
90541 acacacacac acacacacac acacacacac acacacacaa acactattaa gacgcagcac
90601 gccacagttc tgtgaaagga gaatggagtg tttacccttc cagctgctcc tctcctaaga
90661 tgagacgaag gttcttcagg aaggacaagg agaccaaggc atgagaatgg cggatcttca
90721 cgtagccggg caccacctcg atgagcccca tgaagttctc caactccgag gcaatgttat
90781 ctagagaaag aggagtccat gtcaccgagt cttcctctg tccaggtggcg cactatactc

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FIGURE 6KK



90841	agattcacac	acactggtgt	ggatgcgaag	gggaagcagg	tcttgcggtg	gggaattgca
90901	gtgagaaggc	tggcatagca	ccaaccgtcc	ctgtctccac	tctccgcaag	ccacaccggg
90961	acaaggcctc	tgaggcggga	aagcagactt	ctaggaggct	ggctgctgca	gttgccaagc
91021	tgattaacag	aacgtgaaat	cagaaatgcc	aggctgctaa	ttagccccag	ctgacaaatg
91081	gaggcaacat	ctcttagata	tgctcagtga	caggcagtc	tggctccaca	gtgccatggc
91141	aggactgggc	aaacctgtcc	cagcctggta	agaatggctc	ttgctggacc	tggagtcca
91201	tatttaaaga	ctccatttag	ggctgcagga	aaacactcca	atatcacagc	aatgatgcat
91261	gcaggtagtt	gatctatctt	tccccaccct	ggatcgagac	agggtttcat	gtatgctaga
91321	cttaagatga	ggctgaactc	ctgatcttcc	tgcttctctc	ccctgatccc	tattcctggc
91381	ctgcaggcag	ttttgttttg	ttctctctct	ctctctctct	ctctctctct	ctctctctct
91441	ctctctctaa	ataatttctg	catctctaa	ttttctatcc	tgtctcataat	tacttctgta
91501	accagaaaat	tgccaggaaa	agttcagta	gtaacaggac	cgagagccag	tgaatttctt
91561	ttatcgtgct	taccacacct	tcacatagca	agtaacataa	actttgggtc	atgacaaaat
91621	tctaagacta	taataaatta	ggtgaatggg	atttttatta	tatctgattc	ttgaagggtg
91681	atgttggtgaa	agtttctcct	atgggttgat	ataaagaaga	ggacaaaagc	cttataactaa
91741	gtctgagcct	cacagagctc	cctcacttgc	aaaatacata	cagtgcctagt	tgtatgtaag
91801	ggctacaggg	aattcaacct	gaaaaaaaaga	gtggctgagg	ctaagcctgt	gttttgttcc
91861	ccaagaattg	aatctataac	ccctgtgtgc	aagacaagtg	ctctggccgc	cctgaactca
91921	ctctgtagac	caggctagtc	tcgaattcag	agatctgcct	gcctctgcct	cagaagcact
91981	aggatgaaag	gtgtcttcac	tgtgtagacc	aggctagcct	cgagttcaga	gatctgcctg
92041	cctctgcctc	agaagcacta	ggatgaaagg	tgtcttcact	gtgtagacca	ggctagcctc
92101	gagttcagag	atctgcctgc	ctctgcctca	gaagcactag	gatgaaaggt	gtcttcactg
92161	tgtagaccag	gctagcctca	agttcagaga	tctgcctgcc	tctgcctcag	aagcactagg
92221	atgaaagggtg	tcttcactgt	ggagaccagg	ctagcctcaa	attcagagat	ctgcctgcct
92281	ctgcctcaga	agcactagga	tgaaggttgt	ctgtcaccac	acccagtaag	taattcttct
92341	tcattgggctg	aatttcccaa	tcacattgat	ctcccatgac	aggaagatat	aaaaacagta
92401	agggtttatga	attttaaaag	gcattgtctg	ggatcaataa	actcaaagaa	aattaataga
92461	tctgggtatga	gcaaaactac	aatttgggtta	ttaacataag	ggtcagcggt	cttgtgtggg
92521	gaacagggcc	ctccattgtg	gaagggtaga	gaatgggcaa	taaaaactaa	ggacttgggg
92581	gctcgagaga	tggctcagca	gttaagagca	ctgactgctc	ttccaaaggt	cctgagttca
92641	aatcacagca	actacatggt	ggctcacaac	tatccataat	gagatctgat	gccctattct
92701	ggggtgtctg	aagacagcta	cagtgcactt	acataataa	aatcaatcaa	tcaatcaatc
92761	aatcaatctt	aaagaaacaa	acaaacaaac	agacaaatgc	ccaagcctca	aaaactcact
92821	accacaaaaa	accccataaa	gaaaaaaaaca	aacaaaacaaa	aatccaaaac	catacatata
92881	aaaagaaacc	ctaaaccaaa	aaaaaaaaaaa	aaaaaaaacaa	caaaaaaacc	caccttgttt
92941	ctattacctc	tacagactaa	gaatataatt	cacttattta	acaaataact	aggggcaagc
93001	aatccactat	aaataaagag	gacactttgt	ctctgaagta	aagaaaaact	ttctttccct
93061	aaagattttac	cagtaaagat	taaaataata	gtcttctgcc	tatagtattt	tacctcatga
93121	aactactagt	agctcaacct	agaagttcta	gtggcaggaa	ctgaagggca	tctatctagg
93181	ggactttctc	tgtcagttca	agactagaga	agataagatt	acagggtctc	gctgccacca

FIGURE 6LL

93241	tgggagatgt	tgttcatgaa	tacaattctg	aagcaacatc	ccaggagcgc	tgtctacacc
93301	aagtgaagaa	agggagtctg	caggctcaga	ccacagcttg	aggtgtggat	ggcacatctt
93361	tctggctctg	agaggtaaaa	caggagatca	ctctttaate	tttcctttgc	tcagtctcct
93421	caacggaggc	aagcaaccca	aactctggcc	ttacagaagt	gtggactctg	cagcagctag
93481	catgagccag	ccatgggtct	gagccatcag	aggtgtgtgt	gtgtgtgtgt	gagagagagt
93541	gtgagaggg	gagtgtgtgt	atgtgtgtgt	gtgtgagaga	gagtgtgaga	gtgtgtgtgt
93601	gtgtgagaga	gtgtgagaga	gagagagaga	gagagagaga	gagagagaga	gagagagaga
93661	gagagagaga	gagaacaggc	ctttcctgcy	taagatgtga	cttaaagaaa	gacgagggct
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93781	tggattttat	gtttccgaga	aactcacagg	ggaggcgtca	cacaagaggc	ttacttacat
93841	cccgtgctgc	ttttctaagc	ctgtattctg	cttgtgacta	aagggacaga	gccagggaaga
93901	gcatcgacgc	aagtaaacca	agaagcggct	cagccactgg	tctgggtggg	tggagtactt
93961	actgcctctc	cggatgttaa	taagcagatt	gcccttcagg	atgggtgcac	cttggagcat
94021	ttgagcagaa	gtcaccgaat	cgatggtttt	cgttttcttc	tcttcacgcg	cgcagacttt
94081	ggggcagggg	ccttcgcagg	ggatacagta	catgctgggtg	aagataaaga	gtggacaaaa
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94201	agaaaagtaa	ggaggctttt	tgtttgttat	tacagcagca	tttcatgaaa	gaaccaggct
94261	gaaacatcca	aacaatcaca	cagtataatc	tcctaccagc	ggcaagccat	ccaagctgca
94321	aacacacaga	gggaacacag	actgcagaag	aggaaagcat	gtcgcttggt	tttagacaga
94381	atacacttcc	catgcaagaa	gcatgtgggt	atcataggct	tgtggctggg	gagccagctg
94441	gtctacctgg	gagacacaga	ctcacaggca	ctctggggct	ctgaataaat	ggagctgctc
94501	actgatgaga	ccctcgcctg	cctgcacgcc	agaggagggt	gggcaagctg	gcagcgctgg
94561	ggaagggaca	gccgcacctt	tgtcactaac	aggagtctaa	ttcccaaagc	ccagggagag
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94801	ccctcagtgc	cacacacaac	ctggagccag	aagcagtggc	atgcttctct	cttcctgccc
94861	atcatttagg	aaacggcaga	gaagatgcta	agcctggggc	tataccttct	gagaccttag
94921	cctgtatata	gaataagggc	cgagaagctg	ggctcgattc	tgaatgagaa	aaatgaccca
94981	atcttcttga	atgggtggga	cagtgttata	ttcaaattac	tgtctctaaa	tgagtccgtg
95041	aaacctcacg	aaaagaaaga	aaatcagggt	aaagcaagag	ctgcctttac	taaagtcttc
95101	catccgttcc	caaaatacta	tctatagtct	gttttggtta	aaaaccttaa	tagttctctg
95161	ttatcttctt	atttcctatt	aggagagtgg	ggctgagggt	ttcacaggct	cccatgggaa
95221	gtggacctag	ctagccaaag	tgggggacat	ctggcttctt	ataataccac	atgcaacatg
95281	cttgtgggtg	tggaacgaga	atggcccatc	agactcatgc	atgtgaaggc	tcagtcctta
95341	gctaacagaa	ctgcttggga	aggattagga	ggcgtctggg	gctgagctct	cagttatttc
95401	cttcaactcc	ccatctggga	tcctgccctt	tgaatcaca	agccaaatta	gacatacttc
95461	tgtatacgca	gctaaggtca	tgacatttta	tcacagcact	agagaagaaa	ctaagacagc
95521	tctcatttct	agcctggaga	ggggtttcct	tctgaacttt	ctttgtgctc	tgtttgtgtt
95581	tttctcattt	aactacatga	cgcataaaac	ccagctctct	ctaaaaacaa	acaaacaaac

FIGURE 6MM

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95641 aaaaacatac ttggaataac tgcagcttca tacacagacc cgtgcagaca gtacagagca
95701 cccgtgtact ttccacccaa cgctcccaac tgctgtctaca tccaacataa cgataacaca
95761 gtgacctggc acgcgtgtca ggttctgtgc atttctccat ctgtctacat agacctgtaa
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96121 tgtcctcact tcctggtatt acaaacaaag aggctacaga caagtacatg aaataaacgt
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96361 gagcacaac agtattttca aaatactttc aagcaagtgc taaataggct tcaaaggcca
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96781 ggcgttcccc tgtactgggg catataaagt ttgcaagtcc aatgggcctc tctttccagt
96841 gatggccgac taggccatct tttgatacat atgcagctag agtcaagagc tccggggtag
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96961 ttttctctag ctctctcatt gggggccctg tgatccatcc aacagctgac tctgagcatc
97021 cacttctgtg tttgctaggc ccctggcata gtctcacaag agaccagctc tcctcttac
97081 cagccagctc tccttgtctg ctcccagccc cagaaggag agcattgtctg gactgtgggt
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97201 cccttttcta tgctaaaagt gattatttag atgtaaagg cctctaaagg cttatctagt
97261 aacagcttag tcaacagctc aacaaggtag ggtttactag aaggcctgtc tgtccttggc
97321 acatgccaaa agcaatggac ccaagagcta aaaccaacct cccccctct cttcttcac
97381 ctctctctcc tcctcttcct cttcttcata aactgatcac cctaagtatt ttgttacagt
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97501 ttagtagact gtattataca attctgagtc attgtagtcc ctggcttacc aaatcattta
97561 aaaatatttg atcttttct ttttactgtg ataatgggtc agaaattaaa caggtaggaa
97621 tttacttttc atcttagtat tatgaaagaa aatgtaatct ttggtttgat ccagcagtca
97681 gcttacagtt agagacatct ccaaatacta tagcagcaat ggaatttctt tttgaagatg
97741 tactgaacat cttttataga gagtgactgt agcaaaaacta tacattttat atacttacag
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97861 ggaccttcta caaggtgggg actggatcca gggcatctca caagtgtggg cagtattcag
97921 aacttcctag ttgtattttc agaggctcag aaatgtgtat gtgtgtacag taccggaggc
97981 agggaatgaa ttacaatgga accttcccc aaagtcctct gctctgttca ggggaggaaa

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FIGURE 6NN

98041	caacaacctc	agacctctga	ctgtcctgtg	tttccagagt	tataaaatcc	tgtcttcacg
98101	aacatcaccc	atgacgagtt	tgtggaagta	cagcttggtc	agtcagaaac	agctctgctt
98161	ccacagtga	gcctcagagt	ccaggaagga	aaaccagagg	ccacaaagat	ggtggaaggc
98221	ttagagaaag	gaggttcttg	cagaaaacat	ggcagatcag	actactagtt	catgcccaga
98281	gcccaggctt	gcaatgagac	atgggagacc	tgtttccagg	cctcatgaat	gctgggtgagg
98341	gttgtcttca	ctctctctca	gactgagagg	caaagctttc	actggcctag	agtagcaagc
98401	tgggaaggag	tatctgtagt	taaagtctcc	accgctcatg	cttcagcttt	gcaggtgcac
98461	ggggagcaag	gctcgggagc	acctggccag	caagctaatt	cttacgctct	agtgtctagca
98521	aggcacccctc	aaagtttaga	aataaaaaag	caagctgaaa	cagacccacc	actccaagat
98581	tcgcattaaa	acaagctcag	ccatcacccct	ctgacagacc	catctgggtg	aaccctctggg
98641	aggtcctaca	cttaggggct	atgcagcaga	gaaccctcct	gggcctaggg	acaagagccg
98701	ctgacctctg	ggtgctgttg	cggatgaagc	ctgagggaca	ctcctgcatg	cactcatcgt
98761	cgtggataac	gaagccatcc	gagtcactgc	tctcagcggt	ggggatgttg	gcgcagaaat
98821	cgcgatccac	acagcgccag	ccctcgaacc	tgtaggtgcc	aggcgggcag	gcaggcacac
98881	acacgccttt	gtagtagtag	tgtctgcagg	ccacgcagg	tgtgttgctg	tccggtgtgt
98941	ggcagctgcc	caggcactcc	gggtggcagc	actcgttggt	ctcgggtgag	gctcgtctcc
99001	cgcacacact	tgggcacact	gtgaggacag	agggagagag	ggtggtaagg	atgatgggct
99061	acacagcctc	ccctgggtca	tccgctgcc	ccaccagcgt	ggcgtaccgg	agactggcta
99121	gaaaagcaca	cctcctctga	aatctgcgtc	gatcttaccg	tctgtgaatt	ccacttgggt
99181	aaagacacaa	cccaacccaa	gtccattctc	tcctttagac	tcctgggttg	ctatgggatg
99241	agccattaac	atttaacacc	catggactct	tcaaaatgca	gtggccacac	ccattaaaag
99301	ggagcccatg	gtactggtga	acagagagaa	atacagacaa	tatgggcctc	taggactata
99361	caaggcactg	tgctcctcag	ctctccttct	gtatgagaat	tccattctaa	gaccccagtg
99421	gatgcctgaa	ccacgcacag	aacactggcc	tgtgcacacc	cccttctccc	tcatgcatac
99481	aaagtgatga	agagaggagg	cataacaagt	acggtgggtt	gaaggagaaa	tgtcctacac
99541	aggttcatgg	atgtgaacac	caggccgggtg	gtggtgggtc	gtttggaag	gttacagagc
99601	ctttagcagg	gagctggagg	aagtcctttg	ctgggggtag	agtttggttg	gggttttaca
99661	gcctggccca	cttctctatt	tcctgtgtgt	gggtggaatg	cgatcacttt	gtgtttcctg
99721	cctgacaaga	ctaaagccat	tccttccccc	ctccccccgg	ccaccacaag	gactctgtcc
99781	cctctaggac	tgtacaccaa	gataaacctc	tatctctggc	tccatttttc	tgtcaaggta
99841	ttttatcaca	gcaacaggaa	agttccaaat	aaaacaggga	actagtcaaa	acctctaggt
99901	tactgcagca	aatgttaacc	atacccttta	caaaagcact	gcgtgactgt	ggcctctctc
99961	ttctcaaact	ccagaaaaag	aaatccaggc	tacggaggga	ctactctttg	ccatgggcac
100021	agaagtaatt	atgggtctcta	aagaggacaa	agctacaatc	gaagtgccca	gtgcttatag
100081	aaggctcttg	gtaatgcccg	catctgcaac	gtctcttcac	aacacaacct	tcagatcaca
100141	agcaagctgc	tggacggtac	aggatggtag	tacacagggt	ttctgtaccc	agggggccacc
100201	tgctataagc	cttggttaagt	taaaggccag	gtccagtaat	cacagatcta	aaatcacacc
100261	ctgaacagg	actctgtctat	gcacttctgt	aaatatgtca	tgatgaacac	acgcctatga
100321	tccttacttg	tgaacaacat	ataaaacaaa	caaacaaaca	aacaaacaaa	caaactctggc
100381	taacagtaca	tgtacccaat	tgggggaagg	gattgttttg	aaatactaca	gaactacata

FIGURE 600

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100441 aatatgtata ttttaactgt gatgtaccaa agagtcaaga ttccatgttt tattaataaaa
100501 aaaaaaaaaact actctaaaac caaaactaag ccaaataaagc cccagtaacc acagggttaac
100561 ataaagaaca cacaagttca tctgcacca aaacagccgc tttgtcaacc cttcatgacg
100621 tggctcttcc cgggttcttc ctgtgcacag gtgtatgact acacatacct gaatgtttaa
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100741 cgctacgtct caccgttaca gctgtgcccc agcatcaaac gcgccctcca tgccacaca
100801 ttactgttcc atgagtacgg ccatctttgt gggcacctct gcacgccact gggatcagtt
100861 ttcagaactg actgcacgga gtcagtatgt gctctggagc cttacaccag tctgtctaca
100921 cagctctaag tcacatocaa gaattcctgt gtcactgcc ttaaaaacag ttaaatcagc
100981 agcatgaccc agtaaggaga cgggagtct cgtgacactg ccaaatcgac ataactttgc
101041 atttgactct aaagtcattc ctccacagaa acatcggggc atttcccctc cctgggttatc
101101 tccccctgta ggagtcttag gtgttctgtc gggatgctc tttggctcca aggcctccta
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101221 ataaagcaaa agttttacta gagcttctcg gaacactcct ttaaaaatac agtgtgtgtc
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101341 agatggaaca tgaggcaaca tagtgagttc aacttggcct ctcaagatgg ctggtgtctc
101401 tagaccagtg gttctcagcc tgtgggtcgt gatcctcttg aggggtgaca tatcagacac
101461 catgggtatc agatacgtac attatgattc ataatagtac caaagttata attatgaagt
101521 accaacaaaa taattttatg gttgggtcga ccacaacata aggaactgta ttaaatagtc
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101701 acctatcttc agagccacac acaagtgaag acggaaagcc ttctcagctg gtttatgacc
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101821 cagaagttaa ttatctctgg tcacacaaaa aaacaaacaa acaaaacaaac aaaaaacata
101881 aaacaacaac aaaaacacca aaatcaaac caaacaacaa aaaacctgca ggagccccta
101941 atatcagaat tcagacactg tctaccacag caattacctc aaagacagta aaatggagtt
102001 cactgattta acagcctacc atgtttttag cttcacacac taccactgat tcttttttca
102061 ctcaaacaca tcaatatatg acacagttga agatgatagt ctgatgactt aattaaacat
102121 atgcaactgca cgggttacat caagggttgg ggtctaaatg agcactgaag ttattttgtg
102181 taattttttt ttttttaaat ctgtcaatga cagaagtcaa cgatctgttg gcatttacgt
102241 acccaccag aatttactgg ataaacgctg cacctgtgtg ccaggcaact ggacatcctg
102301 tacaattgta cgggtggcag ccctgacctc aaggaaagga taccacacca ggaagcagg
102361 aaagaccag cacagggtgt tctagtact gtgggttctt ggaagggtct tcagagacag
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102481 aggtcctcag atgtaaatac aggttgagat gttgctggaa acaaaatgga ccagctcagg
102541 gaggtaccac aggcacaccg attgacggac agcaggaaat caccctgctt taggcaaggg
102601 ttaggttctc acactagaaa ggtcagcatg ctgtatagcg aaggcatgat aaccagagtg
102661 ggcagaaggg cagaagaaca gccagaggag aggaatctgc tactgattac actgtccatc
102721 tatggctcac acagatacat aaagttcaat gtaactcgct aaaggctccc tgggtcagct
102781 gtcccagcca tccgccaaca ccattgctct gtgattcggt agctcgacgt tatcagcaga

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**FIGURE 6PP**

102841	gattatcaat	gaggactaga	tgccaacttt	ggagcccttt	acttacttac	ataggaaaga
102901	aatgataca	tcacaataga	tgatgaagtc	aaatagctac	atagtagtca	aagcccatac
102961	catataaaag	cagggggaaa	taaccttgta	cactgtcttg	aatcagttac	cccccaaatg
103021	caaatgctac	atctttccag	gatgagaaag	agaaatagaa	atccttgaca	aaggatttgc
103081	taaatttgag	acatgttgag	ccctgttcca	ggcctgtgat	gggaacttct	tctcaactaa
103141	gaaccataaa	gttaaaaaa	ctgtctttac	agatagaacg	gttcttttaa	ggcatatacc
103201	agatccatga	gtcccttaac	actcagtgat	gccaaactgtg	aacaaatgcg	catctgatat
103261	tctgtgggtg	gaagaggaca	aaaaaggggt	atgcagagag	ggagagagaa	gatggaggaa
103321	ggccgacctg	cttgctaggg	gactgactct	agagatctgt	gtgtggctac	agggaggaaa
103381	gggggtgtggc	tctctctcca	gcacagagga	ttccaggagg	aagcaggaga	acgcagggct
103441	gggattagac	agtcctggag	ccagcttcag	aagcctgctg	ttaaatttgt	ctcatctcga
103501	tgtatataaa	tattattagt	gttcaggact	attaagggat	ttcttgaaaa	gcccctgcac
103561	gtgctgtctcg	ccagcagatg	gatggctgct	ctccatgagt	gccaaaactt	aaaatttagt
103621	gcagtaacca	aatttccaat	tacagcacca	tggggggaaa	ggaggggacc	tcccccgcca
103681	ctccagagga	ggggcacaca	ggcatgggta	aagggcagtc	caaccttaaa	aagaggaaac
103741	ggaagctgtg	aactagggca	cgaaggaaag	caaattgatt	ttgcccatga	gaccgttcta
103801	ttccttgcca	ttaatcagcg	aagacaataa	aaacaaaacc	ttattgaaac	agtcagaaaa
103861	gctacaacat	gtcctgtgtc	agccatcaga	aggacaggtc	cagggtcagc	gtgcatacgg
103921	aggccacacg	ttttaaact	cctcttcatt	tctttaagag	aggacaaaca	gcccctgcac
103981	atcagcttgg	tccttgcat	tagtaagttc	tttctaattt	ccctttagcc	cgtgattgct
104041	tctgtcagtg	aatcctttca	tgatcgaaag	ctccgagaag	cgagcaagct	aaagcttccg
104101	agtccaacgt	gggaagaaga	agtaacgaga	ccgcagaaga	gaaggatgga	agcattagac
104161	aaggcagtg	aaaacactgg	tgggaacaca	gaggccagtg	aggggaagggg	gaggtaacag
104221	gtgctctggg	tgactgtcag	agcccatggg	gagtaagggt	ccgaacatcg	tattcaactg
104281	tagtccaaac	tctagaacag	agttaaaaag	ccatttgcta	tcagtcctga	agtcctctctg
104341	gcaagaatct	tcatattatt	tgaaacacca	cacctaggat	ttccatgggc	ttccccagtt
104401	cgaaactaag	ccaacaagac	ctgtcttcag	gctctagtgg	cctacctcca	aaggaacctt
104461	tctcatttca	ttaacccaac	caagcactct	atggaggagt	gtgtggataa	gccttgaaat
104521	agactcgtgg	ctaactcttg	gagcatcctg	cccagtactt	aaacatgcag	aagcctcctc
104581	cgctcctgcc	ctcctcttct	ttttctttcc	tcctcctcct	cctgtttctc	ctgctcctgc
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104761	ccaaggcaag	aggacatgta	atactcaggg	ccgtcacatg	tatttggtta	taaagattta
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104881	aagaggatgt	cagatttctg	ggaaactgga	gttacagatg	attgtgaaac	attatgtttg
104941	cgctgggaac	ctaacctggg	tcccctgtaa	gagcaacacg	tgtgaataac	cactgagcca
105001	cctccccggt	ttcctgataa	tgtacttgta	agactttcca	gacacaacca	tgggtaccagg
105061	agcccaaggg	cagagtatca	ccaaggctgg	ccatgccttc	tgttttgtcc	tcagggttaac
105121	cagcaaggag	gatgctcatg	atgctcccat	gccttgctac	ctttcaggaa	aggcaaagat
105181	aggccaggga	actcaggact	cctcatagtt	tggatggaag	ttccagtttt	caaagaatga

FIGURE 6QQ

105241	gtatctctgt	tggcaggaac	tgtgcctgac	tgaggaggag	caggggacca	atggcaagaa
105301	caaggagaaa	aagcccagct	gggggtctgt	gctgtgtcca	ccttacaagc	atcacaatgc
105361	tttcagttta	ttagtcttca	atgtaccct	ccactatctc	tcttcacata	cctttcccca
105421	ctccaatctc	ctcatataaa	ggtactacta	tgacttcact	gtacctctga	aacaaaaatt
105481	acatggttga	atttgactat	tgtcattatg	gtgtggtggt	aagactaact	aaatctaacc
105541	aaaccaaatc	taatctatgt	tggaggttaag	gcctttggga	gagaattagg	attgtatggt
105601	gtcactaggg	tgggacatca	ttgtggtagt	agtgccttta	tcttatatat	agagagagac
105661	agagacagag	acagacagag	caagcaggca	agctcagcaa	gtcatgcctt	ggccatgccca
105721	taatgcaata	ggaatgccct	ccttagagac	tgacactaca	tccttggact	tctctgtctc
105781	cagaactatg	aaaaagtatt	ttctttataa	actaaccagc	atcaggtaag	ataagtatac
105841	ctcataagga	atagatgggtg	agtgttgctt	cttggactca	gtcagtcact	gggttacatc
105901	ctagcaaaat	ctgtggctca	actcacaaa	tcaaactaaa	tagtgcttct	ccccccgcc
105961	ccccccccc	agggggaggg	atcgaggggtg	ggagagtcag	agacagagta	agaatgagga
106021	gaaaggagaa	tgctttctcc	aaaaggaaga	caaggaccta	aaacatactt	atgggtctttg
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106141	gtgtctaaag	atgtctgcct	ggaagactgt	agccactgca	tagtctgtca	cacagcaaaag
106201	gcaacttcac	gtggcaaaaca	gtgtcttaaa	agcccaggcc	gaaaaatcac	attggtaaaa
106261	gtattctctg	cctaattgcc	aaaaccaaac	caaaccacac	cataccaaac	caatccgaac
106321	caaacgaaag	caatctcctt	ttgtggcggg	gcggtaggca	gatccagagg	agacgtcatt
106381	ttaagccaga	atccaaagct	atttcagttt	ctgtttgaac	agaaaggctg	ttacagatgg
106441	agaacttcca	cagagaaaag	cggaccctga	gcagaacact	cctggagcac	agcaagctgg
106501	acagagagag	gacaggaccg	cgtgcttttt	tgacctgttg	gcacgctagt	catgagagct
106561	cctaactttt	ccagcagctg	atgctgtaag	tcattttctc	cttattgact	ttcaaaggat
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106681	tgggcagttt	cttgattctt	ggggagtata	taaagggcta	taagtcacat	attgttgctc
106741	ccctttggct	ttgccctttg	tttccacac	cttgaaagtt	gcagggctgc	tctgcaggca
106801	gcatggtcca	gtcacagacg	gccagagtca	caggcaggtc	cccatcttaa	ttccaaatac
106861	atctgcaaaa	cccctagaca	gtcttccaag	cagcccaagg	gaagccact	gtttgcaggc
106921	ggtgcccctc	aatgcggaga	cagcactcat	ttggatctgg	tttcccagg	gaccttccgg
106981	cagcattcac	tcctcagggc	tccatgaagg	tctggcacat	gcggggcaag	gctgctctct
107041	cccacatgct	tgcaacccta	ttctaacagc	acaggatcat	ttgaatcagt	gtggaatatg
107101	ctgagactga	aagatgtggt	ctgccacggc	tagggtaact	tgctcagact	cagatctcaa
107161	aagtaaggac	atgcccacac	tctgcaggct	cattctgagc	ctctaatac	tgagatctcc
107221	caggtcagcc	tttccacaat	agctgtctga	gtctctctta	tataaatcca	atttatacca
107281	caaaggcaaa	atacaaggct	gcttattaat	acggagttaa	ctttcagtg	tatttcccat
107341	atgcctgatg	acactttagg	tgtgttactt	atatgcatta	tttaatctc	ctgataatca
107401	caaagggtag	gcacccctca	cttagagatg	gacaaactgg	agacatcgga	gagattaaag
107461	aactcatgca	agaggatcag	gctgctgtgc	cgttgttggg	tgtcacactc	agagtcccca
107521	acagatgaca	gcagcctctc	cacacatctt	cccatcgtgg	tgtggacggc	ttctgagcct
107581	ctctgctgtc	tgaaaggcat	gctgcagggg	agttgcttgc	atgctagttt	tctttttaag

FIGURE 6RR

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107641 catgcaacca taaggaagaa ataaaccaa agccctacta cccttttcta ctctcttgag
107701 gtatatccct aaatctagag gacaaaacaa agtaacatac acaccgaaga gccccgcctc
107761 gtgcatacaa gtgatactag agaaataata tgtatcaact cagtgtcctc tattgagttg
107821 tagccaatgg aagtctcatg gacatttttc tgccacaaat ttaaaagact agattttttt
107881 tttttttcat gagacagggt ttctctgtat agccttggtt gttttggaac tcgatccaca
107941 gaccaggctg gccttgaact tagggatcca cctgcctcca ttttcagagt gttatgatta
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108061 ctgcaaagtt gcacactaac agagaagctt ctcttctgaa agatgcacag tcaacatggc
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108421 tgtcgtggaa gaaaatctga gtcagggcca gttgagatgg ctcagtgggt agataaaaca
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108721 gacagaaggt aagccacaga gttcactgct tgaagcatct gggaacattt cattaatgag
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109081 gcacattttg taatatcagc ttacaaaaca cacacacaca cacacactta
109141 aaaaagcaga aagtctggtg gttttcagt tcttcgtaga gttgtgcaaa tactgccaca
109201 atcgacgtta gaatttttc atcatcccaa agcaaaaagc ccatacatag caaagcttcc
109261 cccagctctg gggaatgact aatcttactc gtctccactt ctccactgaa tcgctgccca
109321 ggagcatttt acttagtgga atcaaacaaa ggtgtttctc ctgtagccac tgtcttccat
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109681 tgtcacagtg ggcataatct gtagaggaat tgtcacctac agtgtggact gtgtctcccc
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109861 atggggagag agaaaaggaa gggcaggaga gagtcaatgg aaaagatggg gacgaagggt
109921 gcagctcaac cttagagtcc ttttaccagc actatattgt tctcacagac tgtcttaatt
109981 cccgtgtact tttaaatagt cgaaaacgcg attttcaacc tattttaaaaa cccacataca

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**FIGURE 6SS**



110041	aatttgaaaa	actgcaggca	gattttaaca	caggggagaa	aacaaacaaa	gagagctggc
110101	atgggggtca	ggacagacag	ggccctcaag	ctgatggggc	atgggtcagca	ggggaggggca
110161	gcttcatggc	tgttcaagg	atggagaatc	tctgtctcac	aaaagtcaca	cactttgtcc
110221	tcaagagttc	tgaaaaaagg	aaaagaagca	agaagtccct	gcagagggcc	gactcccttg
110281	cagccgttct	cagcaggctt	gagcacataa	agatcacttg	tgactgcctg	tcacagatgc
110341	tcaaatggac	aggatgggga	aaaaaaatc	ccttcacaca	cttaaaaatt	actctaagtt
110401	attttaaatc	tggaaactgt	tgtatattcc	ttataagttt	atgaaactca	cacggctcgt
110461	ccatgactaa	ctgaagcgga	attgagagag	tagtctctat	ttataacttc	tctgcttggt
110521	cgtgcgtcca	gccctatttc	cattctctgg	tactgtacgc	agagttatgt	gaagccgtgt
110581	gggctctgaa	atgctactta	cttcctaaca	aggcaggcct	gtgttccata	ggggcaaatc
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110701	ctcaagcacc	catcattgct	caggcagatc	tttctgtgtt	ggttttgttt	gtttgcttta
110761	ttttatttat	ttatttttaa	gacagagttg	ctttgtaaac	cctggctgtc	ctgggacttc
110821	ctctgtagac	caggctagcc	tcaaattcac	agagatccat	ttgcctctct	gcctaccgag
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111061	acttgatttt	agtgggaattg	tgtcaccaaa	gggtgcaagg	ctttaacagg	tcatgcataa
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111361	catcaactgt	aagaacagct	gctctaaggc	tgccctagtc	tagtttggaa	gaaaaaaatc
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112141	cagctagacc	tttaaattat	ctaggagggt	agaaaagcat	tgtccctgat	aattgtacat
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112261	gttaaaaagt	acctagaaaa	gagaccatgc	aactgttgag	ataccatttc	tagaatctct
112321	ctctttttct	gagtgtgcat	gtgcgcacac	acagacttct	gttggttttc	attgtacttt
112381	gcttgaattt	tgtgagcaga	gggggtggaa	aaaggtacca	acttggctaa	aacgcacgcg

FIGURE 6TT

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112561	tactgaagg	cattcaaatg	tcgagatgcc	acgctctttt	ttaaaaccat	tttttaaaac
112621	gattaatagt	tgagcactta	ggtgggcagc	ggtggcatgc	acctacaatt	gcagcacttg
112681	ggaggcagag	gcaggtggat	ctatgtgagc	ttgaggccag	cctagtctac	agatcaagtt
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112981	attatctcct	gatctcagat	aatctggttt	actctaagg	gctgtccaaa	tcatcaagt
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113161	acagggcacc	tgcatagtcc	tgtgatgtca	cctgacccca	cggggctggg	agcagggag
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113281	cccaggtctc	ccttcacac	ctccagacat	gttctggaat	acctcttagg	ctgggtttct
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113401	ataaacctga	accccagtaa	gcagacagtg	ccagcccgt	aagcatagat	gagtctggaa
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113581	ggcaatgtca	aggacacg	aagtttagtt	gctacacaaa	gggactgggtg	cctatacagc
113641	gatgcctaag	atacaggacc	atattttcca	aatcaactta	aatgtgcagg	tgtgtgtgtg
113701	cacatgtagt	gcacgtggaa	gacaaaaggg	caatgcagta	tgctttccac	tattgtctctc
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113881	atctgaactc	agcttctcac	acttgcaaaa	ccatctctcc	attcctccaa	atcaactttt
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114481	tcccacggcc	taggaacgca	ggagagagga	ggaatggcca	ccacaagtct	ggggtgcatt
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114661	tcttcacttg	gcagatggag	aaagtgaagt	tcaagcaatc	taagcgagga	agggtgtagt
114721	gctcgctcac	tactggagg	gggggtgggg	ggagcttgtt	caagcttcca	aggagtgaac
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FIGURE 6UU

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114961 tcacettgta aacaagcaag atcggctgga tgagtgtccc ctaattacgg tttccttggt
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FIGURE 6VV

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118381	actcaacttt	gcttcagctt	acattataaa	cgctgggtgt	agcatagata	cagaagctct
118441	ttcctgtgtg	gtgatgaatc	attactcaca	accaaaccac	gtgaggaagc	agggcccctt
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119521	gacctgcctg	ccgctgcct	tccctgtctt	tgaggtgggt	acaactcctg	ccaccccaac
119581	attttatgtc	acagcttctt	cttcagctga	cttgaaagct	ttatttttgt	caaggtctac

FIGURE 6WW

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119761	gaactggcca	gaatcagagc	cettgaattt	tatgcactgg	tccagggagg	tcctgagaga
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121501	tgagtacact	gtcactcttc	agacacacta	gaagggggca	tcagattccc	actacaaatg
121561	gctgtgagcc	accatgtggt	tgtctgggaat	tgaactcagg	acctctggaa	gagcagtcag
121621	tgcttttaac	cactgagcca	tctctccagc	ctaattatca	tctttactga	taactaaaat
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121921	ctgctcctcc	tattacaagg	aaggatggct	taatggcctt	gctgggctgg	gcttctctgac
121981	tgccaaacag	tgtggaaggc	tgcacaggca	gtggagggaa	aaaaccccca	aacctctgtc

FIGURE 6XX

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123001	ctgttgacgg	gtcacggcag	ttgggaacac	ttttcctata	gttccagaat	tactggtctc
123061	ctacccaac	ctcagatcat	cattaagaca	tgctaattgtg	tagcgagaca	ggttggagg
123121	atctttttct	atataaaaata	ctgtgagctg	gggcgtggaa	cccctgtcct	attgggtgct
123181	gtggccatgc	aaaaagaggg	tcttccaaaa	atttaggatt	aagagggcat	ggtgggagag
123241	gaacaacaaa	ctttggaagc	cttctcaatg	tactgtagaa	ttaaaagcca	accaaggcaa
123301	ggaaggtgcc	ttccaacctc	gaaatccagc	caccctctgc	aacgagccca	ggcctgctgg
123361	agaccacgtg	aggtggtagt	gggtatgcct	ggaacctaac	ataccacttc	tagtaccgcc
123421	cagctggcac	ccaatcagga	gcggcacagc	attctctaag	cccagggttg	cacctgcaat
123481	catcttaagc	atacaatggc	attgatttcc	acttaggggtg	tagaaataac	actcagaaat
123541	tttacctatc	tctgctgttt	tgctgcctaa	tttcaaatc	tctccaagaa	acgcaaacac
123601	aacagaacac	ggaggatgtg	acacacaaat	tctgcacaa	ctcactgcca	atacctcgat
123661	gttataactc	gtgtattaaa	tgggaatcaga	atcctgagtc	ccactgtcaa	acttcctcct
123721	cgtctagtcg	gtatgtgtga	ctgacagctg	atgtcactga	atgcttgatg	tctgaaatgc
123781	ctaggattcc	tttttctccc	cccatccaaa	tataacagct	ccatttcata	ctccctagaa
123841	tttcatttgt	gactgggttag	cacactatca	gtgaggggaa	acggggggtg	caggaagctc
123901	accgtcctta	cagatttctg	ggagggagct	caagagtaag	taagtgtgta	agccttcata
123961	gctctaccaa	acacatgcat	aaaacctgat	taaacacaga	ggaagaacat	aaatattctc
124021	agtcttctaa	ggggcagatg	aagtcctgggt	aagaaggact	aaagaaaaag	catagagtaa
124081	aattcgctcc	cgctttttta	taactcttta	agataaggag	agttgtttta	tgttttcaaa
124141	ataggcagag	agagagagag	cgagctagag	agagaaaagta	tgtggtatag	tttatgtgtg
124201	tatgtgatgt	gatttatgtg	tgtgtgagtg	tgtgtatgtg	gtatgggtta	tatgtgtgtg
124261	tgtgtgtgtg	tgtgtagcac	tgtgtacagag	tgtgtgcttg	gcatgtgaaa	tccctgggtt
124321	tcaatccttc	cccttcagaa	tgtttccttt	ggaacaaacc	aatacatctg	gtgacgctga
124381	ccttttagtgc	ccctcctcca	ctcaccctgt	tttctacagc	aaaagtatct	acaaaaagga

FIGURE 6YY

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124441 agccgtgcct caggaagtct tcaccaaagc ttgaagagca tggagagaag aagtaagggt
124501 ccatcagatg ccttgtgttg aggtaagtcc tccctcccaa tcaaccacaca atgaatatct
124561 tctgatgtca gcccctctct ctgagcatcc tgtctctgag accttggag taagacttct
124621 gtgtctggga ccaaaactac tggggctatt ttggcagctg agccctctgc ctcccttgca
124681 gggaaaaaca gtaggaacat ttcaaataac attcatattt gagatatatt ctggctctgc
124741 gtatttttct acttcatagc acgtgtaatt gtccctccctg ataaaagtgg acctagcact
124801 gctattttta aagttttgtg ttctacactt taaaaggata cacaaagtcc tagcaggaga
124861 acgtcaatta ccaagtacaa aaacaaaaca aaacaaaaat aggaaatcac catttggcca
124921 atgccacagc aatgggtgtt gaatgaggag gggaagaaat aatgaacagt gtgttttagag
124981 agtcccgaga tctgtctcaa agtacttctt aattagagat aaaaaataag atgttaagtg
125041 acgagaggac cttgcagaga cagcattaac caagtgtcac aattacctaa gcatggggca
125101 tcaggtgccc tggcaggctg acgtactaac tcttcacagc aggaaagagc acaggaggct
125161 gtgtgtgggg ctgcaaggaa tgacctccca tgaagtacct ggatcgagct actgaagtgt
125221 gggaaaagtg tcccggaaatc ggagaaatca aggaggacag gaatcagagc tgggtgggca
125281 ccgtcctctg atcaggaacc acaaatggca caagagaggt caaagggcac tgggaagaag
125341 gggcagatgg tggcagtaca gtgcagggtc taccttcatg gttcggacag cttcacggg
125401 gttttgtaag atgctaatta gaagatgtca gacacctccc acccccacgt gtgcaaaact
125461 gaagcagaaa tatttcatat aaaacaaagt gttttttttt taagtctcta aggtaaataa
125521 aagcaactta gtgacatatg gaacacaatg tccccgacag tttgacaata aggaacact
125581 cttccttcgg gaggagagaa atctctactt tgcgtaggga cacatcaagg atatgcttct
125641 ttggaaggctc ttcaggctgg cagagctggt caccaatggg gatggtgtgg gggcggttac
125701 gttctcacia ttccccatct atctcatggt accctccagt gcaacggaag tggagggtac
125761 actgagtgtt catgaagaga aagccgttaa cgagatgctc aacgagaata taaccatctg
125821 tcgcacttgt cccgcatgtc ccatgccctt ttccctaggct gcaagcacgc aagtggtaga
125881 cagatacaca cccaggcaaa acatccatac aaactaaaca cacacacaca caccctttt
125941 gggtcctttg gagtccctgt ttatgggagc agacattgtt ctgtcttctg tcacagatag
126001 catcctctga gcttggaag tttaacatga gattgatccc actctttcca agggggagag
126061 ggagactaat gtgtaagcag acagctccca gtatcacaag ccttagtttc ctcatctatc
126121 actatgtggt ggtagtgagg gcagtaaaaa gaccttgta agctttgact agaacaacct
126181 gagattcttc attctgggag tagccttaaa tgtaactata ttcactggca aagaagaaca
126241 aactaaggcc ccagggtgaat gtaagaaggc taccattttt acttcgggtg tgctgagtgt
126301 taaggcgtgt atagcacaa acagaggtagc tccaccgcaa agggatgcac tgtctctttg
126361 gagtgcagggt gccccctcca ggtaatgaga cagaaaggag tggatacagc tggccagggt
126421 tcttggctgg ctccgagagc tatgctaagt cctctgaatc aatggtaga cacaagttag
126481 ttctctgttg agctgggtgtc ttacttcac accagtgtct atctctaact cccgagctca
126541 agaaatcctt ctgcaggatt ggagagatgg ctacagcgat aagagcactg actgctctcc
126601 cacaggctct gagttgaaat ggctcaciaa ccatccctaa tgagatccga tgcctcttc
126661 tggggtgtct gaagacagct acatgtactt acatataata aataaataca tcttgggtt
126721 ggagcgaacg gggctgggga gagagacgaa aaagtgtctg aagatagcta tagtgtactt
126781 atatagaaat aaataaatta aaaaaaaga aaccttctg cacagccttc tgaatagctg

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FIGURE 6ZZ

126841	gggttttcagg	cttgagcccc	cttttagagac	aggcagcaga	gacacaaagg	cctgccccaac
126901	atgtgtagga	ttagatagcc	tgggtatggc	tgaagggaac	aggtactcag	gttggccccag
126961	gccaggagcc	agactctagt	atattatgca	aggttgcctc	ctaaattata	atgcactttca
127021	tttgacagaga	gtccaacact	agactcaatg	tgtctggtag	cccagagggt	aacaggctgt
127081	gttcttcaca	gggaacatct	gaggacagag	acggaccaag	agggctcttg	acggtggctg
127141	gtggttaagga	ctaggagcgc	ttacggcgag	ctgcttgga	gaagcctttt	cagggtggtta
127201	tctgagagaa	ggcacaggaa	gtcatgaaat	taggacctga	ggacttgtcc	aggataggcg
127261	cagtagtgag	aactgcatcc	ttgtgaagat	gggtttgacc	tctgctggag	gctacaatgc
127321	agctaaatgt	gtctttatct	taatgactcc	agaaacgcca	tgctgtgaaa	gaagcaggta
127381	ggtagaggga	ggtcaggaga	gcaaaccaac	ctcacgtgaa	gggtaactca	cagacttgtc
127441	gttcactttc	cagaacccaa	ccctcaaaag	aacatacttc	taggggtgtag	ctgggaacca
127501	ggaagcagcc	agctctgagc	tgctgcttgc	ttgctctctc	acacagtggg	aacaagcaat
127561	gctcatctct	tttcaaagca	ctccaagcaa	ataaacacct	gcagaggagc	tgatggagac
127621	agacttctct	tactggggtg	agtctattaa	acagaaaagg	aggcataaaa	atgataaacc
127681	cagaccgtca	gaacacagtg	agtgcagaa	actgtcagca	gagagcgaac	tgcttccttc
127741	tcacgccgga	gggcactgct	ggattaagca	taatacaagt	tatgtatgct	cgctgatgtt
127801	cctgagcggg	taagaaataa	ccagtgttca	ctagagtaaa	aagtgcagcg	gttctgaatg
127861	catgctggaa	agatctccag	caagggaag	tgcaggaaaa	cgggagcaga	agtctcagcc
127921	ctcggctctgt	gtatcacctg	gtcacgcttt	ctcactgagg	gatattggtc	ccggggcatg
127981	agaggagagg	ttcctgctac	ctagtgaact	tctcaagact	gacttaccac	taacctgtct
128041	cctatagtgt	caggagcttg	agtctgaaac	agtcttcact	aaatttttgg	ctgtaactga
128101	aactggacta	agtaattaaa	aaggtttcaa	tatttaagct	cacattttaag	ttgggaatgg
128161	agggatggtt	tgatagtga	gagcactggc	tgctcttcca	gaggaccag	gctcaattcc
128221	tatcacacat	ggaggcttag	aagcatcttc	ttcaggagaa	gacctacagg	ggaactaata
128281	tccttttcta	gtgcacacat	ttaaaactga	ggcttagttt	aaaccctgtt	ttaccagggg
128341	caggggtgtc	tgtgcacaag	aaagacagac	agagtttagt	tttagttcta	gacttctatt
128401	tgctcaccag	gaaaataaca	ttggtagact	ttaccaaata	ctgcagcaaa	aactaaatga
128461	taaagtgtact	ctcaaaacag	ggctcaatat	cccacagggtg	atcagggtca	acttttccag
128521	ggaccctggg	gtcagtgggt	tttatacttg	gaatgagaac	acagtaaagc	tgggactgcc
128581	aatattcctg	ctaggactct	ttattttctt	tatggcttcc	cctagcttat	ttagaagaca
128641	ggcttctgtc	cctcaggggac	tggacttctc	aagagcagaa	cactgctgta	ggaaacagtg
128701	tcttccaaga	gtcaagggaa	ggaggaatgc	caccactgag	aggagatggc	ttgctttcct
128761	ccctcaagaa	aagagtgagc	aaggctccat	ccacggcgtg	ttccaacacc	ttcccacata
128821	gctggaccca	gatgtcatag	gggacttgca	gaaagggaagt	ttcaacatca	gctagccttg
128881	gcagatgctc	ccaagtcgtt	caaaaataaa	actcgggcga	tgacggtaaa	gatgggatga
128941	cggcttaaga	tggagcaaga	ggctttcccc	gtggcgggcc	tcagcttagt	gctatgcccg
129001	cttgccgtct	tgttcaggaa	caaaccgggg	cccagatgag	aaacgcgctc	gcgttgacca
129061	tccagaaagg	cagagtgtgt	gcttctgaag	gcagtgttct	ccagcctttc	taccttccat
129121	taaattggtg	agtctgtcct	tgtgtggatt	gatgttattt	ctaaagcaca	caattcattt
129181	caagagggga	gaggcaggat	taagctggaa	atagtttttt	ttctatttag	aaaaaattaa

FIGURE 6AAA



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129241 gtgtaagtgg aaacgttttc atgaaaatgt ttttatatct caacgtttcc tgcgagcact
129301 ctgatcccaa tatatcacag gactgagctg gatgagggag aatgaaggca aaatgaattt
129361 aaataaaatt gaaactgacc ggctaggctt tattctccaa atctcatgaa atagcaaagc
129421 tgagggggac agagccacaa ataaaccaaa agaaaaaaaa aaccacaaac acaaaaaaaaa
129481 aaaaaaacaa gaagcaactc aacgctttca gctcaaatga gtttcaattt tatttcaaaa
129541 tgttttaaaa tctagtttat tttcatagcc acaaaagctt ttgaatacct atgaatcaaa
129601 agccatttgg cagaaccatg gagcttgctc tagttgcttt ctctcaaaact cttccctggg
129661 cctgttaacc ccttgttagt cagtcacgca cagcagggtca ctctcagtac ccagttctta
129721 ggggcactct acagccttag tgtgtatgag caggcagagg ctctaggctg gacggcacat
129781 ttttaaaata cacattttta agtgtatgta ttttttttta ttagtcttaa ataggatagg
129841 gaaaatgata tatacagact ttaactacta attacttttag acaagaaca aacagaaaaac
129901 aaaaaacaaa aacaaccccc tccccaaacc caaaccaaaa aaaccactaa aaaacaaaaac
129961 aaaaaaaccc caatccacat cctttagaga ttattttggt aatctgcac ttgatctgtg
130021 ctgctcaggg gccacaggag gccacaggag gcctctgaaa cttgaaacag ttaagattaa
130081 gtaaaaagtg caacgaagag agctcaccac atcctaaatg tttctcaact actcaactcc
130141 cggtaccac acgcagggca gacacagggg atctgtcgag gcacaagact acagagtaac
130201 agtgcaggtc agacagaaga gcaggggtgt ggtctcagtc cagctctcac atagctcatg
130261 ctggcctcaa tttcgccatg tctctgaaga tggccttgaa ctgatcttcc ggctcccttt
130321 gggactgcca ggtgtgtgtt actctacaaa ggttacgtaa ttgtcaggcc tttgtgtttg
130381 tgtgcatttc cctaagcaac ttcatgtaca aagctaagtt gggatgcat tctctccca
130441 ggccctggccc cttactctct accgtaaaat gcttcttccc taacaacccg acttgagtgg
130501 ggtccctacg tacagagaaa ggagatatat acagaagaaa gggcaaatga ctgcttttac
130561 agggaaagag catcccaggt caacacacgt accagattgt agagagggca ggtgtctcca
130621 tccccgtgcc tctctatttc ctttccaaca ctcagccctg tgtgagcaga gtagtaaggcc
130681 cctctttgat gctgcacccc cctattataa gcacaatgct tgaaccaaaa cagatgggtg
130741 gatgtttggg aaatgactga atgaacaaaa agaagaatgg tattctgtta aacaacagcc
130801 aacatccctc tagagcctgg acacacgtct ttatagagcc tggatacaag tctttatatt
130861 ggatagcaac ctctttactt tcaaatgcaa tctcagagca acccagaaga ctgattcagg
130921 tagtatacca cagctcagtc tcttccatgc tcaacaatgg ctcttccaa atggcattag
130981 cgttgtctac atatctgtac agtcagagct aatgtctatc tgttcgtctt taaatggccc
131041 agagcttttc actttccata tactatttca cctacccttc acctggatat tgtctataca
131101 ataaagagga ggaaaccaag gcttgggcga aactgacttg ccagatcaca tagagttata
131161 ggtatataaa tggaaaagct ctggtaaaga ttacagacta tgctgattct attagctggc
131221 ttaggacag ctgaatggat ctcttcaag gaagggtcatg atttgtaagc atcccacacg
131281 tcagtgtctg gtaaggctcc taagtctctg tggcttgctg ccagccagta gacctctcc
131341 aggggtgaggg aactgggcag agctcagcac aaccagctc acctactgt ggctgtcaga
131401 atcattggat cctgcccac atacatccac tctgtggcca tatcccgag cttcacaagc
131461 ttcacaggg tcgggcctgt gtctgcaaaa agaccagctt gagaagacca ggaggtgtat
131521 atcaagtacc actcgttcat tcgttcgttc attcactagt cagaacttca aaccaataac
131581 cccagaagta aagacaaaaa ctccctctgc cctctgggtg cttgaacttc cctcttggac

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FIGURE 6BBB

131641	ccaattccca	cagggttaggg	tttccagaag	ctttcaaaaa	aaaatcactg	atgaaacact
131701	agctctttag	cttagcgat	tatacaaaa	gctgatttcc	gatttatcaa	aggggtacca
131761	aataggaagt	ataaaaaaccg	tatgatcctt	acaggggaatg	gtcaaagagc	agtgatcaag
131821	tccctgattt	acataattct	cagccattct	tttggcagac	ctctacagcc	actaacattt
131881	ccatctacgg	atgataaaaa	gataactctt	cccccttct	gggtgcctgt	cagggtataaa
131941	cttgaagccg	ggcacagtta	atcctcacaa	ctcccccaagg	aagaggtatt	accatgtttg
132001	ctccagatta	agaaagaagg	gtcaggcctg	aattccaggc	atcagaattc	tactgagagg
132061	gaagagagac	agacagacag	ctttcactct	ggcctagagt	gcagagaaaa	ctactacttt
132121	ctgtgggaag	aaaagtcagt	caaccacagg	aatcacagaa	ggatccatca	caagaggacg
132181	ccactgtccc	ttaagcagag	acaggactga	gaagaacaaa	ggtactactg	ggacagaata
132241	tggagaggtc	agcttgagga	agtgccttag	caaatggcat	caaggaggcc	atttccccaa
132301	gtggaacaca	aatcacagac	ctcaccacag	gagccaggta	gcactgtggt	acgcacacat
132361	accatgtgtg	tactgatgtg	gtgggagaca	caggcagagg	tggcagggtg	aaatcaggtc
132421	aagaagaact	gagagccagg	ccggggccac	tgctctgccc	tgcttatgaa	agccagggga
132481	ttaagtcagg	acttcactcg	tgattcaaaa	agttatctga	agacatggcg	ggaagtacag
132541	ctaggtctca	ccacccctcc	ccctcccccc	cagctctgca	tgctcaactg	aggacgtgcc
132601	acttggcacg	ctggcactct	cctacaggaa	aacatacttt	ggctattcag	acgtgacttc
132661	ctggcactcg	gaagctgttg	gcattggaaa	attaacaggc	tgacttggcc	agggaggaaac
132721	gtttaacaca	aatcacagg	aaaagatgag	ccctgagcaa	gcgggagggt	tgagggaagg
132781	gtcacggaaa	aaagaagggg	taagacacat	ttgtcaggag	tcccaggctg	gtaccaagcc
132841	cactgcatga	caaagggtcat	tgagccctca	cagccataca	cagacatcac	ggctttcctt
132901	tcaggcagtg	gacaaggagg	ctaacggagg	tgaacttact	tggcctggat	gaggcagcta
132961	ataagggaca	ggagctggta	cacacatcat	cacaacattc	ttcattacgg	tctctttctg
133021	ccttcaaccc	cttgcccagt	ttgtaacttc	ataaggtggg	gtaatgatgc	caggaacttt
133081	gtagccctga	ggcagaactc	tgccccagct	gtggccttcg	taacctcccc	ttactacaag
133141	cgacacagcc	acctccactc	aaatccatgac	gacagctcag	tatataacgg	tagcgtgtta
133201	catactaact	tggtcatttt	ggggaaagct	gcttgtgtgt	gtaaaggggg	gggggtggtt
133261	tggggcttgg	gatcaaacaa	atgagtaagt	aggaaaaaag	accaaccatc	cactgagatc
133321	ctaaccaggc	tttcataact	taagactgga	gtcttcaca	aactcacaca	ggtagccata
133381	gaagctactc	ctggaaatcc	aatcctggcc	agaacatgct	agggccaccc	acattcctac
133441	ctgcagcaac	cttcctttct	ccctcagcat	caaccctaag	atcctccagg	gctctgtagc
133501	tcagtaactt	tgcaagggtgt	taagtctaga	ggagcccaga	ggtccgtggc	ctcccagtgt
133561	ggggttacaa	ttcctacaac	cttaaactct	gtaaagcgtg	cccacaagg	ccttcagctt
133621	ctcgccagaa	cttcctaaacc	ttgcctttac	acttaacaaa	gcttcctact	aaatatctac
133681	accaaatttc	cgtacattag	tttttctttc	tgcttgtgaa	aggggtggtg	gtgggtggtga
133741	aactagtcaa	gatcgatat	cctctgcaat	accagcttct	agaaaagagc	gtttttgaat
133801	gggatgccac	gtgctgtgtt	ttgccatatt	gcctgcgctt	cctgcttggg	gccagagtaa
133861	cagaaacctt	gggcactggg	aactgttcog	tgccacgcaa	attccactcc	gtatcttcca
133921	ggcaaccctg	tcgcaaataa	ttcatgtcca	ctacgcccct	accacacaga	atacaactac
133981	attgtgctgc	tagaaatggg	aaacctgatt	cagatcagag	aaggtagaaa	aacatttagt

FIGURE 6CCC

134041	tcaacacaat	actgccttta	tgaaaagggg	cgtgcgccgg	gtgggtggtgt	aaatcccaaa
134101	cctgtaagt	gggtagatt	tcaagacgaa	ttttggaaga	aatgcagaa	tcaaaatagc
134161	atccagcttg	actcagacca	gtaataataa	taacaacaac	aaaaaccag	ccagtccttc
134221	tagagctacg	cctgtttagg	ctgcgcgggtg	ctcttaattgg	ccagccagcc	tgttctcctg
134281	ggaaatggtg	ctgctgctac	agcgtgactt	gctttgctg	ctgcaataaa	aggaaaacaa
134341	gcttgccacga	cccaatagct	tccttcagtt	tgtgcctagc	agcggggaga	aaattaaaaa
134401	aaaaaaaaaa	aaaagcctga	aaaggggtcc	tgaggcaagg	tgaatggagg	acaggatcct
134461	agagaacagc	actgccctgc	aggatttttg	taaacagcag	cctgtaatgg	ccacggttag
134521	agaaagaaaa	acagacatgg	agggaaagcgt	gtttacaact	gcagcaagg	cggaaggcgg
134581	agggagggat	tccccggctc	tgcgctcggc	cctcttcact	ccggtggggc	ccccgggttg
134641	ggctgagctt	cagctcccca	ccccaatccg	tgtcttcttg	gggggcccc	catcttgttt
134701	atgggaaggt	tactcctcct	cggtctggtt	gatcgcgtcc	ctaatactcc	agtgctatcc
134761	ttgcgggag	ccagcttgac	tgacaagttc	tgagccaat	cgctggttg	gcccttagga
134821	aaggtggaat	ttcccaacaa	actgattggc	tgagagagag	ggcggggcct	ggtgattggc
134881	gtgttatcc	gagtagaaag	tagtaaacaa	ccttgggtcca	ggggcggtgg	ggagggcgcc
134941	cggtgccagc	tcctctcggc	tggcagggcg	gggtggggaa	gcacccgaga	caaaaggaat
135001	cctggctgcc	acagcgggga	gggcaggaag	ggggtggccc	caaaagtcag	cacctggagg
135061	cgctggttg	agcccccccc	cccccccccc	cgagccagaa	ctgctgactt	taagccacac
135121	atcgtttttt	tgttttgtgc	agaacctcaa	aggttttggt	tccatcattt	tgactcttg
135181	tatggctgac	gaagtcctca	atggaatgat	aaccgattta	gtcgtctttg	tccagaagcc
135241	ccttcctcac	cgtcgaataa	aaatttaaaa	ttgtctttta	cgaaagtgtc	tttaaatcac
135301	acactaaaat	tgttgacta	tacaatacgc	cattaatggc	atgctggtgc	accagacaca
135361	cagctacatc	ttttgatagc	aagtttttagg	agctctgagc	ctattgggag	cagctgggat
135421	ggagaacata	cacaaaaaga	aacaacacat	gacggcggtg	ggaccacttg	ataagaaata
135481	agcgggttaac	ttgccttgcc	catagtattt	ctggcagttc	cacttgaatc	tcccattccc
135541	tcactccagc	ttcaccatcc	ttacaggacc	ccaggcggag	gaaaccatct	gctcttagga
135601	tggggggctc	tgctcacc	gcacataaac	atgctcacia	gtcgtatcc	tgagcaagcc
135661	tcctcaatgt	aaaaggggac	caggaggcca	gccaaagccg	ctctctccac	ttcaatgctt
135721	gttgaatata	cagagaccac	gttgtcactt	ttcacaatca	agatatatcg	gtatcacgat
135781	atatcgataa	cgggtacttt	ataggagata	acagtgcata	ctggccacct	ggcattctcc
135841	tttgccattc	tagtcctca	cctctgctat	ctcctatgga	gcctgccaca	agcaacccca
135901	gtaaatgttc	accccaagtc	acctttgctg	tataaaacat	ggatttaggc	tttccttggt
135961	ccttgccagc	tggtatcaga	ccccaaacca	gtagctactt	tcattgtagg	caccctccct
136021	ctggacactt	tggtctgttc	ccaggctcct	gccagacca	cacacatcat	tttactcaac
136081	gttggttttt	atgctttcta	gactttacct	ctgcctgccc	aggagaggcc	actgttctcc
136141	accgttctcc	ctggcccagc	taccccaactt	cctgcagaag	actgaaattt	gttttcttag
136201	cactaagtct	ctgatagggc	tttaattgctg	tatttagact	ccactcctac	gttaagaccc
136261	tgaacttcct	gaggcctgga	atgggtattat	cttcagattt	gggtcttcag	tgagatggg
136321	cttctactaa	agtgcccgct	gcaaacctgc	caaataattt	taggattctt	ccctagcatc
136381	ctgagtatgc	ctacccctga	aaatcttttc	ttacacacgt	gcaattaatg	tgtttctct

FIGURE 6DDD

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136441 gctgggtcaa caactctgtt ttctctactt ggcaaatttc cactctgcct aaaatcactt
136501 cctctcttgg catacctttc acaacctccc accaactaca ctgtgtacca agagcagaga
136561 ggtctctttc cgttcttact tctctggcca gaattagcta caaaactaga actagcatgg
136621 tttgttggtt aaggaagagc ggagaggcaa aatttcagaa gtgggtatcac ctgtacatct
136681 gcataaccaa cccattgcca tctgtagggg tgaagcagcg ccatgttccg tttgtggctg
136741 tgatggtctc cccctgcttt ctgtctgaag gcctctgtct ctgaggtgga ttcttactcc
136801 cccctccatc tcaatcagag atctctctct ggctcttatg ctatcaactc tgcacatccc
136861 cgattccttt ccaccatgac actgaactgt catctccttt tctatctgac cagtactga
136921 cttgtctaca gtttagtctg tccgccatac agccatatcc agtgttctaa gaattgtggg
136981 gttccacagc tggggctcag tctctgctta cgccctcatg tgacatctgt catcaaccct
137041 ccatctttct aagcctttaa tgggtgaaaa gagtaaacct gtagataaag agtgggtacca
137101 gatcttcacct taagattaca gatacttggt tgtgaataga atttgttctg gtacaggcaa
137161 atgcacgggt taaaatcaaa actaacaaaa tatacagtat attagctggg aacaaatagc
137221 caactaaagc aatgtaaagc tgggagtctg tattctggct caaagcccat cacgggtgagg
137281 caaacatgat ggcctgagct tcaggatgct cattaccaca ctgcatcctc agtcaagaag
137341 cagagagaac tggttcccag gacaggggct ggtgctgcct aagtcttggg cttcccgtct
137401 ttaagttaac acggcccttg gcaggcatgc ctgaagcttg acttttcggg gattacagac
137461 cctatcaaac accataaata ataacaccac acatatatta catatataaa aactataaca
137521 cagaacactc aattggcctt cagtaattgg gctatttttt ttcttttgtt gttcaatgta
137581 ttctagatct gtctatgttt acaaacggta tgtcttctct actaacaaat aggatttcaa
137641 attaaaaagc tgaacagcaa aggagacagt gaagagacaa tctgttagct tttcatctga
137701 caagggatta atatactgaa tatataaaga acaaaattta aatgtcaaaa gaacaaataa
137761 tcaaaccaat aaatgggcaa attaatcaaa tgggcagttt tcaaaagaag cacaaaagac
137821 caatacatat atgagaaatg ctcaacaccc ttagccacca gggaaatgca aatgtaaacc
137881 acaccgagat tcaaattctc ccccatctac aatggagcac attaagacaa ccatcaacaa
137941 acaactggcaa ggatgcaggg ggaaatgtgc ctgtacacat tgttggtgga aataaaaaatg
138001 aagtagttta gatactatgg aagcctatat ggccaaaaat gtgctactac ctcacttcgg
138061 gatgtacaga tgtgatgcta agtcagcaca cgacacatcc acgttactat ccacatcagc
138121 caagcaatgg gaccaggaaa agatgaagga aatgtgatgc acacgcacag ctgtgtcaga
138181 tgtaaggatg aaaaccaaac tatcggcggg aagttaagga gtggacaatc atctgaagtg
138241 acgctggcca gaccaaagcc tatctcatct gtgtattttt tttttttaat gaaaaataaa
138301 gggaggcctt gtacagaggg aggaaatgat acagaaggga aagaagggac aaacagaaga
138361 taatgggtgg taatcaaagc acattttgta tatggatgaa agtattaaaa caagaaaaaca
138421 gccatcttat cttcacagac agcattctgc tctatagata accctgagtg gtccccaacc
138481 ttgcctgtgt gtttaaatca ctgttacttc cccagaagcg gatttagttg gtttagaggc
138541 tatcacgtga gccttgaaat gaaacagtag aaacaaagtc ccagatgatt ctaatgagga
138601 ggcagggttg agagataaca gtaaacctat ttattatccc tctactgata gaacttgtca
138661 tttcagacaa caccatgtaa agtggcctaa tacacctgtc agttcaccgg tgtgctgggtg
138721 tgtctgtggg tgatcatcct gggagaatta ccatgtcaaa gggcacaggc actggtacat
138781 cagaaatgct ggcaaattac attccattac acacacacac acacacacac acacacacac

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**FIGURE 6EEE**

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138841 acacacacac acacacacac acacaccatc ttccagcccc ctctgccaaag tggggctggt
138901 ttcctataga tctgtcatca gaatctgtga ctgaacattt tagattttca agcatggggg
138961 gctgggagga gctctgaata ctcataaaaa ggactttctg atgtgttcta ctacaacatt
139021 tctggttctt ttggttggtt gttgttggtt acacctttat tatgaattca cttagagtct
139081 aacaaggatg gacccatgat ccaacatcag ttaagttaaag agcgtatttg ctccaatgat
139141 ataaaacgtc atcttattaa acaacgaacg gccacatggt ctcacatcta cggctggata
139201 tcatattctg tcccttcaca tactggcacc ttgctagcta tttaatcatt aattacttag
139261 gcaccatggg atgctttaat tatctggtaa tttcgttggg cttgttttagc actattacta
139321 ttatcaccat tattattggt gctattattg acgactgtag agtcagtttg tataattaa
139381 agaaaccaca tagtatttga agtatattaa ctttataaac acaggaagaa ctgacatctt
139441 gctaacattg gttagactcg cattaaggtt atggttctat catttatttg aatttatatt
139501 tggcagcatt ttgttcagta ctatttttct tattaatttt taagcatttt tctctgggaa
139561 aaacttttct tctatgatgt tgtatagcaa attatttgca cactgtagcg ttatcacatg
139621 actaagtctg gcttatgtta tttccagaag atgcttaatt ccatgccctt agaactctgag
139681 catgtatgca catgtgtgaa cccacagggc aactctgggt gctgttcttc cctccaccct
139741 atttcagaca ggttctcttg ctgggctgta gcacaccaat gaagcaaaca agtggctggc
139801 cacaagcccc aggggtctgt ctacctctgt ttctacataa cggagatttc aagcttgtgc
139861 cactgtgccc gtgattttta agatagattc ttcgacttga agtcagttcc ccacatttgt
139921 gtggcaatca tgccattgat ggagctattt gccaaagtcc ctgtgctctt ctaactctca
139981 ataaataaac gacaccaaag gtcttttccc ctactagta tgaagtttat tatttttttt
140041 tattggatat tttctttatt tacatttcaa atgttggtccc ctttctctgt ctcccaaaaa
140101 cctctgtgct catccctcct cccctgctt ctatgagggg gttccccccac ccactcactc
140161 ctgectgggt gcctggcatt cccctagact ggggtattga gccttcacag gaccaaggct
140221 ctctcctccc attgatgccc aaccagggtca tccctctgcta tgtgtgactt gagccatggg
140281 tccctccatg tattgggtgt ttagtccctg ggagctctgg ggggtctggg tgcttgatgt
140341 cattgttctt tcaatggggg tgcaaaccct ttcagttcct tcagtctttt ttctaactcc
140401 tccactgggg accctcattg gggaccacat gttcagtcca atggttgggt gcgagcatcc
140461 acctctgtat ttgtcaggct ctggcagaaa gtactttttg gcattccaaa tagtgtctgg
140521 gtttggtgat tgtatatggg atggatcccc aggtggggca gtctttggat ggcctttctt
140581 tcagtctctg ctccacactc tgtctccaca tttgtcccgg tgagtacttt gtaccactta
140641 ctaagaagga ccaaagcact catacttttg tcttctctct tcttgagctt catgtggcct
140701 atgaattgta tcttggtgat cctcaacttt tgggctaaaa taccaagggt ctaatcaact
140761 caattcaaac caataaattt tgacttgaca tttacaacgt aagcaattca gatgtagggc
140821 atagcactag ctggttagagg caagactgga tatggggagc ttctaaccga agagtggaaa
140881 gtgttgggag aacaagactg agggcttggg gcagtgtggg tgagggtggaa agctaactgc
140941 gtgccttagt gcatgcctta ggaaagtatc tcagctaggc tactatagca gctatgcac
141001 tatctatacc agagaaaccc cacagagctg gacatacaga tgagctcatt catgtctgat
141061 gagctcatte atacacgtga tagccatgat gttctgctga acgttttatg agataaaacc
141121 aagtttctct tttcagagct gtgtgtttta aggtatgtcc ctttatgaac attaaacaac
141181 cagctgtatg tgggtggtgc aataatccca gaacaagagg gctcatggaa gaagggctct

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FIGURE 6FFF

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141241 aacttcagac tagcttggaa taaatagtgc aaccatgtct caacagacaa acgtaactaa
141301 aatatcatct tacaaaacaa gaggtcccg cataaatatc agagcagagc tgcccagcct
141361 tgggtctcatt ccagacctct taacctatga cctcttgggc tgaggtcata gtcggcatag
141421 ggaagtgcct ggctagtaac aacaacacag tcacacatat ctgtcctcaa ggagctcctc
141481 gagtaaacac ctttgctctg atgatgacaa gcatggccac agtccctgtg cttgcagaat
141541 cttgggttaga aagctcccaa caccaccatc ttccactagt tagcctctgc tgttccccga
141601 actgaatccc taagtaccga atgctctcct gttccacaca gaaacctctg agaagcccag
141661 tttacagaat cagagactgg gccattcctc gaagcattgc taaagaactg gcaggagtca
141721 ctcaagttct caggagctat gggaagataa gattctcccc aatgcggttg cactgaaaga
141781 cagggcagta aagaacaatt atgcctaacc ccgatttctc tctgaatcca tttattactt
141841 ctcaatcttag gagagtcact cttgtacctg caccctggcc actactcaga aaaacattag
141901 tgatatccaat gatcccttta gtaactactg gagaagcagc tagctgaagc atgggggaat
141961 taaggaagac cttaggagtt caaaacccca aagtacaaac gcactgtcag cacacggaga
142021 gatctgtttt tttatgcatg ccttatgcaa actggcctaa gctaaaaaat gttataaagc
142081 attttgagga gtaaattttg atttcagggg taaaaagaaa tgtacagagt caaagaatct
142141 ttctgttggc tgataacaga gactccttgg aaaaattgac atttcttttc gagaagcaaa
142201 aggtggagta gaaatagtgt gagcagcata tgatgtcttg tgacaatgca gagaaggcag
142261 ttgggagctg ccactaatgt cgagttttca ttaggctcat atctccaact tttggttttg
142321 tgaggtcgca actcaattgt gtagtaaaaa aaattttagt tccattaggg tgcttttaat
142381 attcactata tctactatga aataggagct tagatgatga tgatgacaac aacagtaata
142441 gcagcagcta ctttgaaaca ctcacaggca ttgtgagttg gagccctgag cactaaccac
142501 tgtaatttgc tatcaggacc actgggtatg gcattcggaa aacggacata tgcaatcaat
142561 gcttgtgaca tgggagaaca aaaccttgtc aaccaactgc aaacagatgg ctcatggaca
142621 acaaaacctt agagaaaaat gcaggaatat cagcggggca gtgggggagga aaagagaaca
142681 ctttccagac tgtatgcata gaagggcctc aaaggccgcc atgacagatg tgttcctgta
142741 tcgggggtcaa caaagaataa agcccatagc acaattctta ggaaaagttg aaatgcctgt
142801 tttgtaaata aaacacaccg acttaaatct ctactactta attttataaa ttccgcttaa
142861 atatgtgtct aaatacactt ttttcccctt gttttgagac atggtctctc tacgtagccc
142921 tggtatcctt agaactagtt atgtagacca ggctgacccc tgacgcgtgg ggaccctttt
142981 gcttcttcat ctggagtgtt gggattaaag acatacatca accagctggg cttaagtgtc
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143101 agacttcaga gtttaccaag tttgaggggc tggccaaatc cttctggact tactgagaaa
143161 ggaacagacc caggacaccg actggagcta cacggtgggc gccatggcgc caggccgaga
143221 cacgtggatc cttcggcctt gcttctgtgt ctcagctacc tcagaggttt gctgtggaat
143281 cactagtatt ttaaacatg caaacgcaat tacagttgaa gcacattctc taggagaagg
143341 aaaaggagat tggcatgtag aagcttcatt aaacttttgg ctttttcaa gctaaacgag
143401 tcttaagaaa agccataaaa agttcccgtt gattgattta aaaacaggct tttttttttt
143461 tttttttttt ttgcaattag cagatctaaa tctacgaaag ggagaaacac gtacggcact
143521 tttagttaac ttctgtctt ctctgtgtat ttcaaactgt aacaattaag actctctata
143581 gacacacgta cagatacaca aatacttagc aggacgtaaa cttctatttt ggcttcatga

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FIGURE 6GGG

143641	aaatggtagt	tatgtttcca	cacacacaat	gaattctggc	agtttattta	caagcagaca
143701	tcccatctgc	accagggata	ataccctcaa	ctatgtgaca	tgetacatcc	ctcctgaaca
143761	cagtagggct	aggaaagcac	tgagaggata	taaacaatgtt	cagggcttac	aatattcctt
143821	cctaattgctt	ctttcccca	cttactgtaa	cgatttactg	gaaagattgg	actaaattac
143881	cgtcttccct	ttatcgtccc	aatttgtttg	catttggtat	cctctccttt	ctcttggaa
143941	ctcccttgct	tttccctttg	tcagtaagtt	aaattgcttc	tctcccccaca	tgcatataaag
144001	cattaatttta	taaaacacat	agctgtatgt	catatctcat	gtaattctat	tttacatttt
144061	accactagct	agacttatct	aacatgaaca	aatagatatt	atttactgta	gccagaatga
144121	gaattatcta	atgccactta	catagccaga	aattgatttt	tgattaatgt	ttaagcgaag
144181	agcaaacaaa	cccactctgct	ctgaaaacaa	acaaacaaag	aggagcagag	cactgagtcc
144241	tcggttcgca	ggcatttcctg	caggcctagt	gcctcagcgg	ctgcagaatg	gggcccttca
144301	ccccagggga	aagcggacca	ctgacaagaa	caggactcca	ggcccagact	ggagtttctt
144361	ctccagcaag	tggtgagtaa	aagatttttt	acttattggg	gggggggggg	agacgggacg
144421	ggactgggga	ccacaaacaa	caacaaatct	ctaaaccctc	tcaggatcag	cagagaattt
144481	catcttgggc	gcccactgga	agtcaaggaa	gttggttaatg	gtcatgtttt	ccttcttccc
144541	tcttggtcac	taggtcagtt	aaaagacaaa	gaaaaaggct	gggcatgggtg	gtgcatgcct
144601	ttagtcctag	cacttagaag	gcagaggcag	aggttctctt	ggagtttgag	gccagcctgg
144661	tctacagagt	tagtttttag	agagctagcc	ttcacggtca	tctgcccaca	cacacacaca
144721	cacacacaca	cacacacaca	cacacacaca	aactgacaaa	atgtaaatca	agaaagaaaac
144781	aaaaacaaag	aaaaacagcc	ctgtgccatt	tattcttata	atctctgagg	tttctcagt
144841	atgaagaaca	gagtgcagtt	tatagttctt	gtccactcca	tttatattga	atatataaat
144901	tattttctaa	gataactata	tacataacca	aatttgtttt	taacaaattt	aatgaaaaca
144961	ttcagcatga	aactaaatag	cagtaagact	ctcagatggt	gtcttagggt	aaaaacaaga
145021	ggagcactcc	aaccttttct	ttgacaagg	ctcttgatc	ccaggctaac	ccgtatgtag
145081	ccgaagatga	cttttaacag	ctgacccagt	cccttcacc	gcttctgttg	tactggatcc
145141	cagggcctcc	acgcaccca	gagaagcact	ctaacaactc	actgccagct	aagctacagc
145201	ccggcctcct	ttggagcact	ttcaacagcc	aaaactgaca	caatacatac	gcatcaacaa
145261	gcaagctgaa	caccaccac	cggtgtgctg	agagaagaga	ctcaaactca	caactttcaa
145321	agtcaccatac	caagcctgat	gatgcaaaca	caacttgaag	tcttattggc	gacgctccgg
145381	atactaccag	ttgctaaagg	aacagagtgg	gactgcgact	gcattctgaa	acattttcta
145441	caaatactca	tcttcacga	agaagtaagg	tgcaagtgcc	tttatgactc	tatttccact
145501	ctagacgctc	aggctcaagg	cagagcgctt	agatcctgct	gcacttccat	aaaaacaagc
145561	ctgatttatg	ctgaaagact	ttaatgacaa	agttgtcctg	atgtgcgtgc	gtgcgtgtgt
145621	gcacgcgcac	acacacagac	acacagagag	agagagagag	agagagagag	agagagagag
145681	agagacagag	agggagagag	agagagagag	agagagagag	agagagagag	agagagagag
145741	aggacctaga	gaacaagggc	ctttgtcttg	ctctgccgaa	gcacagtgag	catttcttga
145801	gccctgattt	agcctttaac	tgatggttct	ggtttggtgct	tcaacagaaa	taattgcatg
145861	actgacaaa	aaaggaaagg	ccaaacaagt	cttaaataat	gattgttggc	gtaccaactg
145921	caccaacctt	ttctaattac	aactctccat	tttattattg	tcaggcaaaag	tgagtacctt
145981	aacttgaaag	gctaagctga	gggggaaaag	cctttttgtc	tctactttac	aggtttgttt

FIGURE 6HHH

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146041 ttataaacac tccctcagtc cccccaaagc aacaggagge aggcacaatg accctactga
146101 ggagtacagc ttttacctcc atgggacaat agattgcttt tctgttagcc cctggggagta
146161 aaaccagctt taatatggat gccctttcct tatcaaagac agcagggtaa tacggggagg
146221 gctgccaagc ttgggttggt cggacttggc aggtatgagg cctacctcgc ttctacacca
146281 cgtcactcaa ggaacagagc agaagaaaca cgttctggaa ctttccagag aggccatcct
146341 tgttcatgta ttctagtcca gagttctact tctctctaca gagatggatg aaacaaaagc
146401 aaaacaacac agagaaaaac cccttctaag ggagctggag ggaggagata atctagagag
146461 aggatgccaa aagtggcttg tttccaagtg acaaaatgca cctttgctgg ggaagctagc
146521 aaggtagaag ccctgttca gaacttttca aggagcagat gaagacaaaa aaatgccacg
146581 caatggggga cggaaatcctc tagatgtcga gaaaaagcag cggccatgcc cagggagcag
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146881 tgtggtccag agctgaactt gctgctggag actgtcctgt cagggaaaagt aaaaaacaaa
146941 ccaacacaaa aatccaggag gtgcagaggt agaggcagag gcaggcgggt ccctgtgaat
147001 ttgaggccag tctgctttac acagtgaagt ccaggacagc aggggctgta tagagagacc
147061 ctgcctcaaa aaacaacaca aacaaaacaaa aacaaaagaa ggggggtgaag aagagaggga
147121 gaaggtgggg cgggggccag ggggttggtat tggggaggga aacttaccct ggtggagaca
147181 gtgaaactgt tgtttgccac tgcctctctt aggtagggtc taactgtact cctgactaat
147241 cttcaacttg ctgtattaat caagttgggt tccaactact cttggaacta caggtgcaac
147301 ccaccacacc atcgaagtct tggcgcacag ctctaggggg cataggaaat ggctttcccc
147361 gtgccctgta gaaatggaac tgaaagctca tcatggcggg aagactgttt tttagctcac
147421 actctcacac tgcaaatgac ctaatgacac agcagggcct ccggtaccat cctcactccc
147481 acgctccccac tccatcctaa tgtttagctca cttactcagt ctaccacagg cttaggtgac
147541 atctgaagga atagcatact ataaaaacct gacttgacca ccacagcatg caagctctaa
147601 ggcaggtaga acatactggg tttttgttgt tgttgttgtt ttttgttgtt ttgtttttct
147661 tttccagttt ctccccctca agatcttcac atcatgagtt atgatactcg ttcattacat
147721 cctcctagaa tggctccagt caagaagaga aggctcaatg acccacccca actgcaaaag
147781 caaaattatc ttagaagaag aagaaaagga atggaccatg taattaaaat tacgaggggc
147841 agtgacttac agaggtaaaa agttaatcac aaggactatc tcaaagccta gtgaaaaatg
147901 gggttttcag aatcagacct gtcaaaggta accacgagat gcaataatgt ggtttggaag
147961 tctgggtgac gggcagcagc aggaacaggt caggaaggg gggagtaaat tgtttgcaaa
148021 atgaaatgca gaatgaaaga ccatttgagc acacaggcat ctactctaaa acctgcaaat
148081 acctcagcct cagtcctctc acggaggact ggggagtgtg cactcttctt gttgctttag
148141 aggaggtctc tgctgcagaa gcagggtggg tgggtagagg ttcctactga aagctacttt
148201 gggatccag cccccgggg ttggtagcaa ggagtccctt taatgaataa atgaagctgg
148261 agctttccag atgtttcatt aatggggcac ccagaaccaa tgctgctgca cccgtgcccc
148321 ctacaactac taccggcatc tgggagcact tagctctaaa gtagggttaga gctggagtgt
148381 aactgtatct atgtgaagac tgagtttgta tatgggaagc tcagcataca gcaaggccct

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FIGURE 6III



148441	acgtgctggc	tatcactgca	atccaggcaa	aggcttcctg	gaaggctaac	gaactataac
148501	ttggctgata	atgccgttcg	ttcatggctt	cgtgagcgct	ccagtcccgg	tggccttggc
148561	gagagttgga	gttgagtggg	gactgcaggg	acggaaactt	ttccagcaag	aaagagtccc
148621	tcttctccca	cggcactaa	ggaggatact	tgtatttttc	caggatcagc	tgagtcgtca
148681	caagaggaga	gtggaggggc	aggaggagac	cgcctcaggc	ggcgacaagg	gagcccagca
148741	cctcccctga	agttgcagcc	agctgcttct	tggctggaaa	cttattttaag	ttgtcctctg
148801	tcccacttct	gaggctctac	agggatgctc	tgggcactgg	gatccatgaa	caaacaggga
148861	tgagcggagc	gaagggaaca	ctctgctcag	atgagtctgc	ctctcaacgc	cctttgccct
148921	cactgtgctg	gtggggagtg	gggggtgggg	aatctgatgg	gcaaaagcaa	ggggcggaga
148981	tgtgactgtc	acgcagaagg	tgtgcccagc	tcttagaaaa	gtgaagaatt	caagaaagca
149041	aacacaagca	tctctcctgc	ttctactccc	tagttatccc	aatcccaatg	aatcttggaa
149101	taattttagt	tactgacact	ccagatagca	tcttcaacag	tgaagccaga	agcagagcaa
149161	agggatctta	gtagcatgtg	ttaattttca	tgcaggatgc	aaaacaggca	tttcaacttt
149221	catctttctg	gatgcagcta	cagtggccac	catccctgac	caggactctg	tcttcacttc
149281	atcctttctaa	cagttatgca	tcaagagtgt	atcagtaacc	atatacccat	gcaggatgtg
149341	taacttgccct	cttctctccc	gtttcaggac	agccagccac	tggaaagtct	gaggggcccg
149401	gctaactgaa	atctgcagat	acgcttagga	atccctccca	accagccggg	ttaacctcca
149461	tatgtttcta	atctctaact	tgtacccctt	gtgcagcctc	aaagagatac	atgtcacttc
149521	ccgcactgat	ctgacaaccc	tctctctgag	aggctcataa	gcaccctttc	ccaaggatgg
149581	tcactttacag	aaagctgcag	gcaaagtata	tccaagtctg	ggcagcatat	aataaatggc
149641	tagtggcaga	taatgaaaag	gctgaaatca	caaaatcaaa	attctttcca	ataaagggtga
149701	atcccacacc	tattcattaa	cagtccccta	ctgtctaaga	tgtttgtgta	agatcaatga
149761	ataagccatg	tcagaagact	tgccgactat	ggaaactatt	tggataatgc	tccaaggggc
149821	tcaggaatag	gacagatcca	atttagaact	gggggggggg	gggaggggga	cactctgtct
149881	ccaggccagg	tgatgaagac	atacccaggg	tcattctttc	accatgacaa	agacatctcc
149941	attgtttcaa	agtcactttc	agtctcctac	aaagtatatc	ggagaatagt	gtgccatgtg
150001	aatgaatggt	caaacttaag	caagggtacc	accttccttt	cagaaacaac	cagagaaata
150061	cgaaactgcc	tctggggcat	cgcaataagt	agctggggct	ggtaagctcc	aagtcttacc
150121	tctgaagtca	tcagtaagca	tgggacagtg	aaggctcaga	cataacatct	catccaagta
150181	atcaagagta	acgccaccca	tcacagatgt	actggtgcca	ccctgggcac	agtgcacac
150241	cgaggggcaact	gtataccctt	cctgaaggag	ttaatcactc	aaatgcacaa	acctaattgtc
150301	acgagagagacc	ccagtttaag	agcagggttat	ggggtcatag	gatgagtgtc	cgttaaaaagt
150361	gacaacacca	tgcaaaatca	gcaagacaag	cagacccatc	acagcctcga	gaagaccaca
150421	cagataagac	acatccacac	gaccaaaagc	tggggaatga	aagaaagcac	gttagtggga
150481	aaactgggtgg	aatttaata	aagcctgcta	agaatattgt	gccaatgtta	gtgtcttggg
150541	tgtgataact	ggattatgat	tatgtaagat	gttaacatga	ggagagctgg	gtgacatttc
150601	aggaactctc	tgtgccgttt	tcaacttttt	ctaaggtttt	tttttttttt	tttaaatgaa
150661	gctgaggagg	aagcagagag	cctgggaggc	tggcttactc	tttagtttgc	tttgtcactt
150721	tgtccctggg	aagtagggtc	attatactac	agagctggct	tgtgttacag	ctcttccgat
150781	tttgctccct	ccatgtcttc	ataacttttg	gggaatcgga	tgttactcag	gtgagacaga

FIGURE 6JJJ

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150841 agatgagtga agtcacaatg tcattggaga ttagagagag aaagagagag agacagacag
150901 atagacagag agagacagag aacaaacttc aaatttataa acacattatt cttccacaaa
150961 ggtccacatc acacactccc cccatttgtg caccaccctt gacaacacag ctgtgtgggt
151021 ctctagaaga tgtagtggga accaactttt agcgtcctaa ggaatgatgt catccttttg
151081 tctataggag ctggttccag aggttttgtg gaacagcttt ctttccagaa agcagccagg
151141 tctgaagctg ctcagacttg ctctagactt cttctgtcta cagagtacgg caacatctcg
151201 tctacaggga ctgcgactgt tccggctctt tgatcatcct gttccctaaa cttacttcc
151261 ttaagttgca aaacattttac tcttgggtgt ttgggtcctt cctcgggtata gaaattcata
151321 ttctctgttt ctctctctct ctcaacgggg ctgtggactg aacttacgtg aacttcttgt
151381 gtttgcctgg ctttactga ccctacacct tcagtccttt tcctttgtac ggagaaagaa
151441 atcattaaag agaaaattgt tccttaaaat catcccttcc cccatcctcc aagccttctg
151501 ctctgaagtc agtaattgaaa aaaagattgt tactcacact ttgcttgtat cagctatgga
151561 tgggttccta cctatcttat tgccaaactg aaaaactact tggaaaatgt tccaatgggc
151621 tcggtagaat aatagctcca agtcagaact ggggtgcatg ggggtgtgtat agtctccaga
151681 gtggggaagg ctggctactt gtcgggtcct gccctatcag cctaccagtt actacgctgc
151741 tcttccctgg cagctcagtc agtgtgcggc gtggtctctc ctcctggcca tctaaaatgt
151801 ctgcagttat tgtaacacag gatgtgattt ttagatcaat ataaacctgg tgaacagatc
151861 aatcctgtcc ctcataaaca caggcaagta tctgggtatc tagacgggtc tgaccttaa
151921 cctctgaacc aaatttctca cccaaacctat cattagcaga ttgagcccaa gtaaatgcat
151981 gtgtgcagaa gtagagggtg actccttctt aactgctagg tttataccag ctaccttatg
152041 ggggtgcccc aataccatct ccaactaaaa ccctttcagt tttaaaggga aagggccctt
152101 aggtaaatgg ttcatttggg gaggcctcct ctctttgagc agtcacatga atccacaatg
152161 gagaaagaga ctctaactcc tgggatttct ggtaacctaa agagtcccat gtctttccta
152221 cacaattggg cccagacgg ctcaagtctt attgaaccga tatatcaatt ctgggtggag
152281 taaaatgctg agtaagagaa aataaagctg aagtaagcgt aaagacaaga gttgttttgt
152341 tttagctgga acatgattct ttgatgagaa aactctcata aacaggaaaa agcacattat
152401 tgaagctgaa gtgtttgatg gcttccattt tcctaagagc atttcgcctt agacacaggt
152461 gataactgtc aagagcagcc agagtgatc ctctggatat ttctaccata aatatttctg
152521 aggtcctact gtgtgccagg gattgtagt atagtgggga tacaagata ggagttgagg
152581 ctatatacac tcttttcaaa ggcaaagtct cgagctctaa acgcacgact caaacacaaa
152641 accatgatat gcaaaggaaa caaatgggtt gtttcttggg gacaggttga acagtaagta
152701 tgggtgacagg ttttaattag aagacttcag aagagcaggg ctgggccatg taaatcaaat
152761 cctatatcag ggtctgtact aaactcagaa agactaactc aggcagttac tagagttatc
152821 atgacccctc acagaagttc atataaggac cctaactctg aaagcagaga tttgttgttt
152881 tgtttttttt ggctgcctct agctagcaca tttatgaaaa acaggttaag ttactggctc
152941 caaattactc cttataaaaa aaaacaaaca aacaaaacag cataagcttt taagattttc
153001 ttttttaaaa cctagaaaac agtctccctg tcaagagcag gcatgattaa tgacttctgt
153061 gctgtaagct tgggtatccg ccgtgttact agtgtgtgat actcctaaca gcttgtaatt
153121 gccccgagga tacttttggg actgaaagggt gtggggcggg gcctaccttc ttaatatctc
153181 cataattttt tggggggggg ttagactaca tttatcaatg ggacattgaa aatacagaaa

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**FIGURE 6KKK**

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153241 cattgtcaag tcatccacat gaaattatga atgcattatc atctgaagag tcatttccat
153301 aaaacggcag atgacaaaata gtcagctctc agtatccatg ggggatgggt tcaagatccc
153361 tccctcagac atgaaaatct gagatgagca agtttcttat tatagatggg aaatctgcat
153421 atgattttaag tttttcttcc tgcatactag aaatcagagc tagatgggtt gccatacttg
153481 agagcgacaca aacgctgcgt aaacagtcaa ccgtacggca ctgcttagag cagtggttct
153541 caaccttcct aacgctgctt ctcaaagtgt gggaatggaa ggtgtgtggc accatgctca
153601 gctagaatcc cattgtaagt atggcactgg ctggacctac atctgcagaa ctccagggtta
153661 ctgaagggct gtactgcatc ctgacagctt cctaggtctt aggaagctac caacctgcaa
153721 actccttctg aggtgaaacc acaacagggc atccacaaaa ctcaaccact ggaacccaat
153781 gaaccagtca agttaacaga aactgagcc accttttctg ctccatgaca gccctgacag
153841 acaacatagg caagctctat cacactgtat ggctcaacca gccatatttt ccatagaggg
153901 gaaatggagt ttgctgcttt gtttggcaga tgcaaagagt aaagtagagg ggaaccaaat
153961 agtcttagag cacttgggaa ggttagctga ctctctagtg tgttccactg taccacgcaa
154021 tcccactatt agctccccac ttctcttggg caacaccaga tctgaacgaa acctacagga
154081 aggtttgaag gtacctggcc ttctaaattg tggcttacat aataacatca ggccctctgg
154141 tagaccctgt aggtcaacaa cctaggaagc caattctctat agtccagctt aaataacaac
154201 cttgtgtttc aagggaaaaat aggaaggtgt ggaaagcctc cattgacacc ccaactaact
154261 tgcctttgct tttctagaga caactatgca cttaagaaaag gcaatcgaga tctgcagtta
154321 atttacagtc actgagatga ctcaacatac gttcatacta gtagtatctt cagcttctcc
154381 agtctttttt ttttaaagta gaaacaaaat gtccggcctg acatttttaa aacctgacct
154441 atgaggaact tgaaatggtc agttttacaa attttccttc ctttctcttc tttcttctaa
154501 gtcattcact gaattatgta actgactcct agaacacact gcagacccca tatggaataa
154561 gacagcacia ctcttgcctg catgatcact gctgggctgc aggaatgtgt taagacacat
154621 gtctgtccct cagtagtgta gacacaatcc ctgtcttgcc ctttagaagt ttataagatc
154681 cctgggcaca cagaacttgt gcatcaagtt aaagactaaa gggccagagt ggggttgaca
154741 agagcaattt cttaagagtc tgaagaaaag gagccagaaa catggagaag gcagtgaaga
154801 ctattttcag cagagagaag agagaatgtt attgagatga aaatgtggat ggcagattcc
154861 agtgcaaggg gtgcagatct catagaaggt gggtcagggg tgtgggggtt gaaaatggct
154921 aacagcgagc tccattatgt cacagcagag atgacgcaag gagctgtctc ccagcagggtg
154981 agatgatgct gggtaggcag gaggtagaca caggaagtgg atttaggaac ccatagcaac
155041 catgagggag aatgaggggtg gaacttaaat aaggagcat ttacgtagaa aagagttggc
155101 agaattaact ccatgggaaa cttagtggaa ctgaggacaa cgtgtcaact acaaagacca
155161 gaaagcaggg ctagttagat ggctgagtga ggaagggtgc ttgctctgac ttcaatcttc
155221 aggagtcaca ttccaggctc tatctccaca cgtgtgctat ggcacgtcca cacatagagc
155281 aaccaataaa ataaacataa cattgaaaga taccagaatg catgctgtct ttgaaaaccc
155341 tattcattgt cttaagtata agatgacagg gccatttccc aaaaccatac atcttgtgga
155401 gacacagggtg gggcaaaacc aggtcaagtt cagtggacag caggtaccaaa atggacttat
155461 ggctatacct ggtaaggcaa gccatgaaga tgatgagttc tggctccctc gttcttcggg
155521 aacctgaaat ctggagaagg gggagggggg aggaggagga ggaggagaag ggaagagggt
155581 agtgggtggc actggtggac agggaagaac atctaggagg aaagaagcta cagaagttac

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FIGURE 6LLL

155641	tgacggcagg	agaggggtcct	tccaggccat	ggaaacactg	ggcctcaaag	gacaggctgc
155701	tccagtctga	tgctgcatca	gaaacccaca	gtcaatatat	tgaaggtgga	aatctgaaaa
155761	gcacttattt	ttataattaa	atacttttat	gatagagaaa	aaagcaaaca	gagaaaaaaa
155821	agcaaaagca	tcaggtttca	cccaaacaca	gcaatgggtca	gtttgggttc	atctgagatg
155881	accaacaaat	gccaatatta	gagttacagt	ttttcaaggc	cataattgct	acatttaaaa
155941	catcaagagt	cacagactgt	cccaaacag	tcagagccct	catgacctgc	ctgtcccagg
156001	atctgagagc	tacagtgttc	tgcttctatt	tagagcatta	tgaatgctaa	atagaaatgt
156061	tcaaaatatt	ttacaaaatg	aaaagtagac	atcagtcac	tgcaggctca	aggctgttct
156121	ccaactttta	aatacattag	ttcttttttt	tcctttcccc	tttttctttt	ctggagacaa
156181	ggtctcaggt	agcccaggct	ggcctagtat	tttatgtgtg	actgagaatg	accttgagct
156241	cccgattctc	ctgcctccat	ggaccaacga	gtgcagttct	ttccccttaa	gagtcacata
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156361	gggctgtctt	gagttcgaag	ccagcagggg	ctataaagtg	agctccaaga	taggctgcgt
156421	tgcagaatca	caacacgtct	caaacaaaca	acgtagcaga	catatctaac	ccttaagcat
156481	gacaacgaca	catttgtag	atacctgaat	aataagaagg	gggtgcatca	ttataattat
156541	tattatttta	cagttgtaaa	catgggaaag	tgctgagcag	ttcaatgagc	ttagggctac
156601	agtcactcaa	ctgcatgcta	gctcagatga	ggataatgca	gaaacgcctg	ccgggaggaa
156661	ggaaggagca	aacacttctg	ccactccgtg	aaatgtcact	caaataacaa	aacaaaccca
156721	ccgaccgacc	tctcaggata	aggaagtgtg	gcggagtggg	aacacactct	tgactgggtg
156781	gtgaggggccc	ctgggattct	gtacctagca	tcacacacaa	aaactgcaaa	caaattcttt
156841	aagccatgct	tggtaaaaat	gactcatttt	gaacctagt	tgaattggag	attatttttc
156901	aattaatgaa	gtttttctag	ttggaaggac	ttacaacaag	ggccactatc	ccaaaagccc
156961	ttagggactt	gtctaaatga	gtaaaaatat	tgtgcaatta	ggccaacaac	tgaaactaag
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157081	ataaaagggt	caaaggaatt	taagtgaact	gggttgactt	ttcaaggcac	tgaggtaatt
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157321	aagatttcct	ttaaacagt	ggtattatct	atttttggtt	ttttctttac	agaacattaa
157381	tttctttgca	aaatgtttgg	ggtacagaga	ttgcctgaca	agagtggcca	ccatgaagct
157441	tatgggacag	tgagaggaga	ggtgaagaag	cctcaatctt	tctgagccca	tttcatctcc
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157561	tcagattcac	aaatgaaatc	tctttgtctc	ccttctgtat	gcacccagca	tctgtccac
157621	ctagctgacc	gttacagggg	cagggccagt	gttaacatgt	caagtgggca	gagggctctc
157681	tgcatctcct	agtacatttc	tggctacagg	tgaactaaat	gacaccaaag	aactgctctc
157741	aaacgtgcat	cccaaggtag	agctacaaag	gttcaatata	accccagtat	tttgagagat
157801	cttaaaacgc	agtcaaagtt	aactgtcatg	tccatagcaa	ggaggaactc	actccttagg
157861	atacactggg	ctggtcttcc	agtgggcatt	tcagagagcc	ctgctttccc	atatcagctc
157921	catcctgtat	cctcaccgtt	gcttccaaca	gggaaccgtc	cacatctgac	tgcccaatca
157981	gatttcagca	ggtggcatgg	gggatccaga	aagcatttct	ctgcaccttt	taactctgaa

FIGURE 6MMM

158041	ctgcatgcag	aacccgtggt	aagaaatgct	tctctgatcg	ctcctagcac	ttttagtggc
158101	catgttaa	cagctaagta	agaatgactc	ttccatctgt	gttaagtggc	cttttaaagc
158161	taattcacac	tatctccaaa	taccctgaat	taccaagtct	gagggctgcc	tagattcctg
158221	cttgtaagca	atagaatgac	actgaggact	ctcggctctc	ttctctctcc	catatcctct
158281	ctggttcact	gagaaccaaa	catcatctaa	acagaacaaa	aacatcagaa	ctgaaggaat
158341	cgccaaagta	tatacacgtg	actcccgctc	gaatgcattc	agatccgacc	agtgactcca
158401	agctttctgc	atgtttccca	tgagctat	gccctgaatc	aactcctcac	cacaactctc
158461	gaaatgacat	ggacctctgc	tggtgcactt	attattcctt	ctctgatggg	gagtgggtat
158521	gactgaaaat	tttcgcgcaa	ccagcctcta	aacagaaatg	cagttttattc	tgagtactca
158581	aattcaa	tcagtaacac	agcaattaca	ttttaaaata	aattctctcc	atgttcttgc
158641	ttctaagaag	agggtttagt	gggatatgaa	gagtcta	ctaggcaacc	atattggccag
158701	gcgaattata	aaccccatat	atgttcacac	atcaagcagg	gcaaactgct	ctgggaacaa
158761	cccttaatat	tttattgcct	gcccagggtg	ctgagcactt	ctgagataca	cctgtcacag
158821	gaaaatacag	cacttccttc	catctttacc	ccatagtgtg	cagacaattg	ggcagagcta
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158941	atagaaat	aaaggagata	caaatgtact	ccccaaaccc	taaatcttcc	tcccacggag
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159121	tagtcattcc	atacattttg	aaaatactct	agcacgataa	attacagtag	ctgcatcttt
159181	catgggtgtt	cacataaata	tcatttgggt	ttcaggaaac	caattacgga	gcggtaaatc
159241	atttttacat	tgcttttcaa	aatctttaat	ttaacttgca	acacggacag	ggcacacaca
159301	ggctcccagg	aagaacgcag	ctcacacatt	gtatcattcc	ctcttgccg	agtttagcaa
159361	caacccctga	gtaagccaca	acaatat	catgttctaa	aatatttggg	ttatatctat
159421	atatttcaca	caggtattag	gctcagcaag	tatttcctaa	cctcctgtag	tatttagttt
159481	tcaagacttg	gggtaggatt	gggaccacat	tgatttcagg	gtgctgactg	tacttctgtc
159541	accatcagct	agtttaagga	caatgactgt	cctggcagac	accgcaaaca	cagagcctct
159601	atgggtgttct	tgagaaatca	agaccatcat	ctcattggaa	aggcgggtggg	aaacaagggtg
159661	cagggccatt	gaggccacac	aatcaacaac	aggatttgct	ccagcctcag	agacacagag
159721	tggactggca	tactatatca	atttgggaatc	ccctcggcta	tgacaagttt	gtgaaatgaa
159781	agaacaaaac	aatacagtac	aagatcaagt	tttagtagag	agaatgcaga	caaccacaac
159841	cgagtactta	gggagaaaaa	aaaaaaaccc	agctcttagc	tggggagtg	cagtcaaggg
159901	gggaaatcac	gcgaaggaat	ttctttcagg	tgcaagaagg	catgagagtg	ggagacaagg
159961	attgagcatc	ttggcagaag	gatcagaaac	ccagtccaag	gtctacactt	cogtggagca
160021	gccgcagaca	agcttaggta	tccggtgggg	ataacctaca	gttaagacat	cacattacag
160081	acactaggga	gccattgtga	attacagcca	acaggtgaga	atcataactt	agcggggcgg
160141	acacaacaac	caagccgtga	tctagagcag	gaagcggggg	atagacagaa	agacaggttg
160201	taatggagga	gaccaagcag	agggctgcat	taaggcagag	gcttctgtgc	tgaccaagtg
160261	actaacacaa	agggcccttg	cagaagacca	gagatgtcag	gggggagaat	tccttctgag
160321	ggggcctagt	tacactagcc	acttgatatt	caccgggaag	gaggcagaga	agctaggagg
160381	gtgggcacaa	aggcagtggc	tctcttctac	ctgaggagag	ctggcagctc	tatcaatacg

FIGURE 6NNN

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160441 gactactcct aaatgggctg cagtcagccc agaaaaaaaa aaaatcactc aatactctca
160501 ggttacctac cctggctccc aaagctgggt atgcaagaaa tattttgttg ttgttttgct
160561 tttaaaagga gacaactgat gcttggttta gtattgtttg aactacatca ctcacaaatg
160621 agagactgat aaagagattg acaagtctga ctctagaagc aaacacttcc agtctgctct
160681 catctgccct ccccaacttc ctccattctc ctggcctct accccacaat atgcttgaaa
160741 atagtaggta actgagtttg tttgtacgg tggttgtctt gttatttcaa gcagggtggg
160801 ccagagagaa aaaaacattt tctggaaaga ttttaactac tggatcataa acaagcgtgt
160861 ggtggccacg cagcaatctt tgtaataacg aatccaagac gtcctgggtg tgaagcccag
160921 tgaatgtaat gttagctgaa aagcaccgcc tgacacacct ggaaatgtgc cacgggccag
160981 cttttagtag tgcgacttca aagggaaact ggagtctact tccgcttttc agtgagttag
161041 aaatgatttt ggctgtattg gtagggcaga accagaaaat aagttttgaa tttgtcataa
161101 taattttaca aaaccaacca acttgtttaag atgcacctc caagcacaac taagctggct
161161 atagaggcta tctgcatttc tgcattcggg cccctggact gctcaggctt aggggtaggg
161221 aagaaacatg acttaagcca ttacccttat tctgtgggca tttgaagtgg ctgccaggca
161281 cgtgacacca actgtttcaa ttgggttaca atgacatcac tttattattc aactctgttt
161341 gcatttcagt ctctctcttt ttccggggac ttgaggccaa tcctggccaa gtcactttag
161401 aagagaaaga agccagtcct aggtagtcac gaagtgccaa gtgtcttttg tgtctcctag
161461 cctagtttgt aagccgggaa ctggtgacat aaagggtctt gtcaacagcg cccgggtgtg
161521 ctgcttccct cgcagcggga gagggagatt gggaaccag tagaagggtg cggttcggcc
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161641 taagaaaact ataaaatgga aaccgcatgc gagcttacgc tggaaacctc tttaaagcac
161701 ttgtacttcc aaaaaaaaa aaaaaaatgc agaaaacatt tctaatttag tcaagcgcac
161761 tcttctttcc tcgagcaatt agtcttaatt catgtcacct aactactatt tctgcattaa
161821 gcaacgtgac ctctagaacc tacagtaacc ccctttctga tggtgaaagt caattattct
161881 gatttttttc atcttcacac aataagttac cagagaataa actaacttca aaaaagcatt
161941 acagtgtcat gtgtgttcgc ctgttgatat gtgcacacat tcatggcacc tgtgggtctg
162001 tatccagctc ttctactgtg cctgtctctc aattttgcag ctcaacctag agatcaccaa
162061 gtggccagcg agctccatgg atcagcccggt ttctgacctc ctctgtacta agattacacg
162121 caatcatgct gagcctctaa gaacatggcc gctcatggtc tgaactcgga tctctcacct
162181 agcatggcaa acatgttagg aacggggcca tttcctcaac acaaaggaaa aaggcttcct
162241 catgggagag aatgactgga tgggcgagta gacagatgaa aatggacttt tcacaccaac
162301 tggttagaga ccctgttgct tccaggcaca aagcacacca gtttctagta tcagtgggtt
162361 gaaatgcatg ttttaagctct ctcatcctta cttggctctt gacaggaaac ttttatgggt
162421 gaactttatt ctgtagaaat gcagtggcat taaccaagca cacaagcca actcaagcct
162481 aaagtgtgcc catgactcca accctacact cattggttct tgccagaggg aacacgaaac
162541 agtgtataga ctcagaactc tgcccaggcc tgtgaggcag ggccagggct acacaccttg
162601 caaacacaca gcaggctctg cccaaggagc gttcactagg taactatcag ggtgggtcaa
162661 gggctgtacg acagacagac cctgcacagg cagggaaagt ttcctggaga cctaccatct
162721 attttcttgt aatctcaact gatgtgttct gccaaagtcaa ctattattta tcatttataa
162781 agcagctcct attggcagca tactctgcat atgtttcagc acttcataaa cctccacagg

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FIGURE 6000

162841 tataatcgct tgtggaggag actgggttgc ctggagctgg aatacagacc cacacgcatg  
162901 tgagcccggtg taaatgcaca catgaccggt ccctaccgct ctttcacgag tcatgtcttg  
162961 gctctgtagg ccgagtatct ataactaaag ctctctacag gtgtcaaate aagcaatctt  
163021 ggtcctctca gatgtcagct aatggccttag agccccccc ccctaacagt tctatcttga  
163081 ttgctaacca aggtatcca ccttagtate atcatcagtg caagagaagc caaactgcac  
163141 acgaagacct ggagagcact tcagagcaca catccgacct cttcctcatc cgagtaccta  
163201 gcaagccagt tttccttcct ctctgtcttc cagaagaagt tccaactcca cctcggagca  
163261 aagcagcagc tgcagtgact agcagtgact atgcctttgt gactgcgtat cactcatcca  
163321 attcacagac tacttagcat cgacttgtat acactttgcc caagaataaa tatttatatt  
163381 cccgaaacac agtcgatcga gagcagctga tacagggtcg gagatgacag aggcagcaaa  
163441 cacaacaag taagacctcc aggagtgtga gggacagggc tagagacaaa gtaaacagag  
163501 gccacaagat cctaggcgct aggtgggggc tactgggtacg taagggtgc tggaaagaag  
163561 agtcctccgg ggactggctc ccacaaaggc tgcccaatct caagtgggtca gctctgggcy  
163621 cttgtctaga tggcaatgct gcgtggactc agtgggttat gtatgcgtgt gtacatgcac  
163681 atgctaggat aataattaaa aataagaggt catgagtttg ggaggttggg gtttgcctat  
163741 gggagcaact ggaagtgggg ggcagagaaa gggctgggag tgacacaggt gtagttcttg  
163801 tgtatggtct aaagattaaa ttagagttag ggaaaaaaa accccacagg aattgggaag  
163861 agtgattccc aagccactga cacagcacag cactgcttgc ctgtggaggt gctcctgtgc  
163921 catcctccct aatctttatg ttgcacatct taagagtggg ctggttgggt atcctctcat  
163981 gcatgtatct cctcagcgtt ctcatccacg aatgcttaca ggtgacgtta gcatcagcag  
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164161 ttgccactct tcaaactgaa ggtctgtgat acttaaaagg gggaaaaaac ccattgaaat  
164221 gcagaaggca gagaccatca ctcaaagata ctcatcgctt ggaggtcagt ttatatattg  
164281 aacagtgact tgggattggc caaccatcac tcatgccatt aaagtaatat ttcagtttca  
164341 actgttttac atgcatttag catgtagacg tattcaattt atagttgtaa acggtctaca  
164401 agtgtaagaa gccgataccg aagcttcgaa tttgtagggt ttttaagtcta agtcccaatt  
164461 cataccggca ctacagggtca gcaagtgtat ggtttttaac ttttaaggagg cgctcaataa  
164521 actcggatag aaaatctggg agcaccaggc cttgttgtga agctactttc aaggcgatga  
164581 tcctcatcgc caggaggaag ttggtttata cccatcatag ttcctttaac acaagcaatg  
164641 cagaatggcc ttcacaagtg tctcctctaa aatgactgtt taaattgtgt tgtttcaaaa  
164701 agaggacatc cacgagccgc atgtttccat tatcccttgg aactggagct acaggcagtc  
164761 aagggttcc ttacttgggt gctgggacac aactctggcc ctcatggtag aacagcaagc  
164821 ccagcaacct ttctagtacc aggtatagggt cttaactttc gtggtctctt gatggcacac  
164881 agaaattgtc tagaagtcag aggtatgta cgggtggatg atgtacaccc agtcgccctc  
164941 caagcaagcc aaatatgaaa gcaatttttt ttttcaaaaa taaaatagca ccacactgct  
165001 ctcccaccag gcgtgtagag attttcccca acaaaatatg acacacatca tatctatgat  
165061 tgcttctaaa tgaagaagtc tttaaaagtt ttaacttctt aagggccaaa tatcaatgga  
165121 tatattccat ataaataaaa attcatcaga tttgtcttca cctattttgg ttgctgtaac  
165181 caaatccatc aaccaaccaa ctaaccaacc aatcaaccaa ccaaccaacc aaccaaccaa

FIGURE 6PPP

165241	ccaaccaacc	aaccaggtag	tctctgtctt	gttccagtc	cattttcctg	gtgcacaaaa
165301	ggactgattt	tacttggttag	aagggtatcg	ggcaattctc	tgtgtctctc	ttacaagggg
165361	actaagcatt	ctcaggagg	ttcaatcttt	atggcccaat	cactccccct	cgccccaaaa
165421	caatgtcttg	atgaccttcc	aacacagtca	tggcagatta	tggctctgtg	gctttactgg
165481	tgccaagggc	tcttgagaat	acaacaccaa	agtgatctca	tcccaagaag	gatgcttcag
165541	acagacagtc	ccacatgctt	tctctactc	ctggctcatc	ccctgtattc	catacatcta
165601	tatccccctg	ccctcttagc	tctcctctga	gtggcaaaga	ggcatctccg	acttaacgag
165661	atgcaaggca	gagttctagc	tccatctgcc	atccccacca	cacacctccc	aaacaaacct
165721	actcccttcc	tcctgccagc	tcgggaacgg	gcaacttcac	ttctcgtttc	atctaagcca
165781	aatgcctgaa	tcacccctta	tcctctcttg	ccccacctgc	aagatttcac	aagtccttaa
165841	atattcctga	atctatctac	tcttagttac	tgttaactgat	gggtgcagtt	ctcaacaagg
165901	aactcctctg	tcccggcact	acctgcactc	agccatgtct	agatacattt	ttcaattgtg
165961	tctgcgtaga	caaggggtag	atgtaccacc	agtatctagc	aggaagatgc	atagacaagg
166021	ggtagatgta	ccaccagtat	ctagcaggaa	gaggccaggg	atattgatag	acattctata
166081	atgcacacag	cagtccttat	catcaaagac	tgtccagctc	aaaatgtcaa	tggcattgag
166141	aaactgagct	ctattccaag	ccagtagaat	ctctccaaaa	aaaccttctc	aaaacaactt
166201	cctaactgtt	ttccctgatt	tttcaactct	aattgtctctg	ctcgatgaaa	acaactaaag
166261	ttatcagcag	aaatacagag	tgtgaccac	tagagtgtt	tgtcttgtgt	catggcctgt
166321	aggcccttgc	ctactccact	ggcccccgcc	cagctcctac	attctcatcc	caccaaattc
166381	ctacgtcaga	gccctaagcc	ctcaggtgac	tctgctagag	acagactcta	cggtagtaac
166441	tgaagggttaa	gtgagcccgt	aaggaggaa	tgagccttgt	aatgggttgt	gccttcatga
166501	aagacacacg	gaagcttgct	ctctcatcca	ctctgctgtg	aagcttgctc	tcccatccac
166561	tctgctgtga	gaagatggcc	atccacacag	aaaaaggacc	tcactggaat	ttgaccttgc
166621	tggaaactctg	atcttggcct	catagttcta	ggactttgag	aaaagaaacg	tcagcagctt
166681	aagccaccca	ggctgtggta	ctttgttgtg	aaagcttgga	ctaatacatt	caaccttgct
166741	accttgccaa	gttccagttc	actggccatc	agtccactta	caccacagcc	cttgccttcc
166801	ctcttctgaa	ctgccattag	ctgaccctta	ataaccctta	gtcaaaatgc	caccctcccc
166861	aggaggggact	gtgttactcc	atccttctctg	gatttttgagg	acagcccat	ggttggcatt
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166981	gtcttgcccc	ttgtcgaatc	aggataagat	aatctgtgtg	gcttatatct	cttaaactca
167041	aaacaaggaa	aggtaggggg	tctgtgaaca	tgctttgccc	catgaccag	ttccctctgc
167101	cgcttctcca	aagagagcta	ccatacttat	gcctacctta	gtttcccaag	agcccatcca
167161	gggcaggagg	gaatcattac	atgtaacatc	tagaatgagt	acttccttat	attctttcac
167221	tttaggggagc	agcaaagggt	caagggttacg	gtaaagtaca	ggtagggggg	catcaccttg
167281	atatgatgaa	gcaccaagga	actccccaat	gttaactatc	tagccacaga	gcaggtaagg
167341	gtatgctcca	gttagtttta	cgagggtcaac	tctgaacaga	ggaaacaaaa	gcaagcagta
167401	aaggactatg	aggcacgtgg	gtttgtgctg	tgtacagccg	agcagtcaca	gatgcctcac
167461	taaggagggtg	gcatggggac	taagagtgac	tggagttagc	catgggaaat	tcaggcaaaa
167521	agcaaggaag	gtctctctga	actggtgagg	aacagcagtc	gtcagtcagt	attactgtcc
167581	gttattttctc	tacactggcc	ccaggcaggt	gcttttgaat	gactggctgt	ttgcaaaggg

FIGURE 6QQQ



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167641 aagtccagat acagatggcc gaatgagggg ccacgagcct gtgcaggaca tacagataat
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167761 gttaacgggtg ggaatttctg agagaatccc aaagagagct agctgggtgc ttgaggccaa
167821 caagggcaag gcttataagt caggggcacc ccagaaagga ggcacacccc agaaaggagg
167881 cagcttctaa gaaagaggaa aagagagaaa gcaggcaagc ctgagaaatc aggccttgggt
167941 ggcctgaaaa ggcagaccat gatgtgtgtg gtgggaaaagc agggcaggac tcctcctcct
168001 tctggaggaa tacatgtgct ggcactggga catccagctt caacccagg agcccaggcc
168061 cagcatgacc tcctaacgca ctgttttagta gacagggtag agcctttaag aatggtggct
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168841 tttacgtgta catcttcagt ttcacaattt gagataaagt gaatacagat attttcattc
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169561 gtgcaagagg aactcaggca ggggtgttga gtttttggat ttgcactta tttatttatt
169621 tattggtggt actctctgtt tattggggga gttgtggtgg gttgccattt gtaacatttc
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169741 agccagagge ttctgtcagc tactaaaggg ttcccttccc ttctatttta tggcctttct
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169861 atgctaataa ggcccctgaa agtcatctgt gagcacatcc actcttgttt aaagagccat
169921 gtaaacagac cacagacggc tacagagagc aacgctgcac agggcaagga aaaggggaatc
169981 tggctgcacc gtacagtgtc acgttgaagt gatttatcac ttatgccagg aggaggaact

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**FIGURE 6RRR**

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170041 gaaacacaaa cgcaatttca agtttaagca tggcgtctcc acaggatctt ccatagcaag
170101 cactctgcac tcgggggctc cctgtcagga aactcctgga caacgggttg tttgccgtct
170161 gatccacttc agttacctca ccaaaccattc aagaggctact ttctgatgtg tgtgggcttt
170221 agcgctaggt tgatacaaaa cagtacctgg atctgtactg gaagtcaact atatttgctg
170281 ccaaattccat tgtaactggc tctgcatgga gccatccgtg tgagagaggc tgatgtgtct
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170461 agacagatgg agacacggat cactggaaga ctgctgtatg gggccacatg gggaaacact
170521 gggttagtca ggaagacacg gcgggtttcta cagggaagt ctgggtgtcc ctttgaggtt
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170941 atctgcttct tatgtttact tgctctcagg ttctgtcac tgactcgagc aagagcaacc
171001 cttaccatag ctgcactatg atgtttggac ttcaaaacca aactctggac attaactaag
171061 atttctcttt ttaaaatcag taatacactg ttgactaaca atgaatgaat gaagcagagt
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171361 ggaaacaggc aagattaata tggaatagtg gcgcaaacca attagctcaa aaatttccac
171421 aaccccatgt attagccctc tgctcagctc agggagataa tgagaacaca taacggaagc
171481 tcccagttca ccaatgcaac tggggagcgg ggggggatgg gtacctcaac cactcttaat
171541 gagtctgtag actaagataa cagaatggga gtcttccatc aacatgaggt aaagctagca
171601 tggcacctca gcctttcaaa gttactgttc actgaaatgt tattagaaaa attgccaatt
171661 gtgataaagc ctatggatca aacactactc ccattgcaag gaacattcat aaacagaaag
171721 ctgttgtcag tccccgaaac ttaaactgta tagagcagag aaaacctgga agaggggaagc
171781 gccataatac ggatgagaaa acagggctag gggctcgtaa atggcagatc aggaaggaat
171841 cccatccgcc ttggagttgg tgatcttgta atgttcagag aatggactca tttcaactca
171901 caggttcggg gtgaccacag tgcttgctga agcaccgtgc ttactgtatg gtgctacaca
171961 agtgaggtct ctcataagct gcagagacac agaaaagtct caagggacag gtgggtgcat
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172141 atggggtaac tgcagcaggc acagggaatg agctaagaca gaccctgggt gagggaggca
172201 gctcatcttc aatgcccgga gagcacaacc tatctgatct gatatactct ccagtttaca
172261 aactactgac aatcacatca agtgaagggc agctgcagcc acagctctcc cttgttcaca
172321 gtttgctttc cttgggttcta gttacctgaa ggcaactatg acataacaat attaaatgga
172381 aaattacaga aataaagtag ttccttggcc tcaagttgcc tgccactgga agttacagga

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**FIGURE 6SSS**

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172441 agccatcttg ttgtcctgct ctgtaagggt cctccctttc tgcaacggat ccaggctgta
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172561 gtacccctga ctttacttaa cagtgacccc caaacgggaa aaagagtagt gttggcaact
172621 tattacagcc aaaaacatgt tattacaatg tatttttatg actgctgtat tgatactggt
172681 aattgctggt tataattaag cttcgttata gatacgtatt tataggaatt agcagcatac
172741 atcaggtttg gtgggtattta tgggttcagg aatctactac agatctttga aagtatctcc
172801 ctcacaggga gagagactac tgtaccattg ctcttcaatg gtgactccta atactggcat
172861 atagacagct ctgctgacct tttagaagtg ccagagaaca ggcactctgg acacagcgct
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1441 ccagagcaaa ggggacataa acaccaggaa caatggagag agagcctcc|t gtgaaagtga  
exon 7 Primer 5

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SNP1507

1561 ataccggccc cctgactaca gggacctcat cagcttact gtctactaca aggaagcg|cc  
Primer 6 exon 8

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FIGURE 7A

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2701 caagctgaac aggctcaacc cggggaacta cagggcccgg attcaggcca cctctctctc

FIGURE 7B

2761 cgggaatggg tcatggacgg aacctgtgtt cttctacgtc caggccaaa|a cgacatatga  
 exon 14

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2941 gctgtatgct tccgtgaacc cggagtactt cagcgcagct gat|gtgtacg tgcccgcagc  
 exon 16

3001 gtgggagggtc gcccgggaga agatcaccat gagccgggag ctgggacagg gctccttcgg  
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FIGURE 7C

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